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THYROID–PITUITARY RELATIONSHIP IN DIABETES INSIPIDUS *

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ALTHOUGH it has long seemed reasonable to attribute diabetes insipidus to hypofunction of the posterior pituitary it has, until recently, been difficult to understand why lesions limited to the hypothalamus can establish the condition and why on the other hand experimental hypophysectomy does not. The modern theory of diabetes insipidus, as expressed by Ranson and his collaborators whose own brilliant researches [1-9] have contributed so much to its conception, goes far toward reconciling such inconsistencies as these and provides at least a working hypothesis susceptible of experimental and clinical demonstration. It rests upon the recent fundamental discovery of a bundle of non-myelinated nerve fibers which arise in various parts of the hypothalamus and descend the pituitary stalk to terminate in the posterior lobe of the hypophysis and also possibly in the intermediate lobe. Detailed accounts of these anatomical studies are contained in the writings of the Chicago group.[1, 2, 4, 6, 7] Their functional implications are at once apparent when it is seen that a permanent polyuria comparable to diabetes insipidus has been produced in the rat, cat, dog and monkey by bilateral interruption of this so-called hypothalamico-hypophyseal tract; (a) at the supraoptic nuclei [10]; (b) along the course of the tract either in the anterior hypothalamus [1, 2, 4, 11, 12, 13, 14, 15] or in the pituitary stalk [16, 17, 18, 19, 20]; or (c) in the posterior lobe itself.[16, 21, 22] That this tract influences the secretory activity of the posterior pituitary is strongly suggested by the facts that experimental injury to the hypothalamic nuclei or to the tract itself is followed by degeneration of the tract distal to the site of trauma,[2, 10, 17, 23] by atrophy of the posterior lobe (Broers [10] even observed homolateral atrophy after destruction of one supraoptic nucleus), and by a greatly diminished concentration of pressor, oxytoxic and antidiuretic material in extracts of the posterior lobe.[7, 8] Presumably the impulses which reach the posterior lobe from the

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floor of the third ventricle are secretory in nature and this form of polyuria is essentially paralytic rather than irritative in origin since the permanently excessive urine flow follows the causative lesion only after a latent period of one to two weeks.[4] If one excludes the transient polyurias observed by Claude Bernard and successors after injury to the floor of the fourth ventricle, on the apparently justifiable grounds that they are due to vasomotor adjustments or to indirect stimulation of the pituitary, the fact remains that permanent polyuria has been produced only by lesions located somewhere along the supraoptico-hypophyseal tract. Thus a reasonable explanation is afforded for the fact that extrapituitary lesions can result in a condition remediable by extracts of the posterior lobe itself, and the clinical portent of such disturbances as skull fracture, encephalitis, suprasellar tumor and basilar meningitis is plain.

Were this the entire story, however, it is obvious that total hypophysectomy or clinical lesions which destroy the whole gland would likewise result in diabetes insipidus. There must be another essential factor, and von Hann [24] is given credit for first suggesting that the disease cannot occur unless functioning anterior lobe tissue is present. In a considerable number of clinical autopsies, all marked by destruction of the posterior lobe of the pituitary, he pointed out that the only ones with diabetes insipidus were those with viable anterior lobe tissue. This astute observation has been supported by those who have consistently produced permanent polyuria in the dog and rat by simple extirpation of the posterior lobe.[16, 21, 22] Although many early investigators reported that polyuria frequently occurred after total hypophysectomy it is generally believed now that these transient increases in urine volume are not comparable to diabetes insipidus * and that uncomplicated excision of the entire hypophysis is not a cause of polyuria.[25]

Thus a state of normal water balance seems to be in part dependent upon a balance between the diuretic property of the anterior and the antidiuretic activity of the posterior lobes. That extracts of anterior lobe tissue evoke diuresis has been repeatedly demonstrated,[26, 27, 28, 29, 30] and Pencharz, Hopper and Rynearson [22] have produced transient oliguria in rats by excision of the anterior lobe alone. In this respect as in others, however, the activity of the anterior lobe is complicated by interglandular relations. Biasotti [28] and White and Heinbecker [30] have confirmed the finding of Barnes, Regan and Bueno [27] that anterior lobe extracts do not produce diuresis in thyroidectomized dogs. Mahoney and Sheehan [20] found that the polyuria which followed crushing of the pituitary stalk in dogs was promptly and completely abolished by thyroidectomy and rapidly reëstablished by feeding desiccated thyroid; it should be noted, however, that these polyurias were not assuredly permanent and that enormous doses of thyroid were used. Fisher and Ingram [5] then showed that the more permanent polyurias following

* Transient postoperative polyurias may well be due to vasomotor readjustments, to the greater stability of circulating anterior lobe hormone, or to unintentional stimulation of the anterior lobe or pars tuberalis, as evidenced by the experiments of Ingram and Barris.[3]

hypothalamic puncture in cats were greatly diminished though not abolished by thyroidectomy, and White and Heinbecker [30] reported that the transient post-hypophysectomy diuresis in dogs was quickly abolished by the same procedure. Heinbecker and White [15] have several times observed that the permanent polyuria caused by hypothalamic injury in dogs is diminished by thyroidectomy to about the same extent as that in Fisher and Ingram's cats.

In two species, then, the diuretic property of the anterior pituitary is modified by thyroid activity, and the rapidity with which urine flow parallels thyroid administration or withdrawal suggests that the mechanism is not wholly explained by variations in the rate of tissue oxidation. It has been claimed that the diuretic and thyrotropic principles of the anterior pituitary are identical.[27] Gaebler,[31] however, observed no correlation between the changes induced in the water metabolism of his almost completely thyro-parathyroidectomized dogs by anterior lobe extracts and the variations in basal metabolic rate; Dix, Rogoff and Barnes [32] found that neither anterior lobe extracts nor thyroid substance induced diuresis in depancreatized dogs despite the usual elevations in pulse and basal metabolic rate; and White and Heinbecker [30] felt that the diuretic and thyrotropic hormones could not be identical because anterior lobe extract, ineffective in thyroidectomized dogs, produced diuresis when combined with thyroid in doses too small to increase urine flow when the thyroid was given alone. Regardless of the exact identity of this diuretic principle in the anterior pituitary, however, it is of further importance to decide whether changes in water output induced thereby are due to a specific water-regulating substance elaborated in the thyroid or whether they are due simply to the generalized acceleration in tissue metabolism. Even should it be proved that the thyrotropic hormone, working through the thyroid, is responsible for the diuresis the possibility still remains that the thyroid itself exerts an effect on water exchange distinct from that on tissue respiration.

Similar studies not having been reported on man or monkey, it was decided to perform total thyroidectomy on a human subject with diabetes insipidus to determine if possible: (1) the effect on urine flow under controlled conditions, (2) whether his sensitivity to pitressin might thereby be increased and (3) whether thyroid and other metabolic stimulants affect water exchange in different manners. We were aware, of course, that species differences might result in a disappointing reduction in urine flow.

There were other but less compelling reasons for believing that ablation of the thyroid might materially lessen urine output. The occasionally striking diuretic efficiency of thyroid substance has long been known. Eppinger [33] described the opposing effects which thyroidectomy and thyroid administration have upon the renal elimination of water and sodium chloride and showed how the rate of absorption of saline from subcutaneous tissue paralleled the rise in metabolic rate induced by thyroid. Dietel and Ditsch [35] claimed that pituitrin and thyroxin exert antagonistic changes in the elec-

trolyte distribution of various tissues, and others have shown [36] how thyroxin accelerates the interchange of salts and water between tissues and blood. Most of those who have studied the effect of thyroidectomy upon the pituitary have emphasized the anterior lobe hypertrophy [25] but Herring,[37] who thought that the hyaline material in the posterior lobe might represent pituitrin in visible form, found this material greatly increased after thyroidectomy, although later [38] he reported that removal of the thyroid did not enhance the physiological potency of posterior lobe extracts. A specific effect of posterior lobectomy upon the thyroid apparently has not been found nor has the thyroid in clinical diabetes insipidus been described as visibly abnormal. Pal [39] claimed to get beneficial results in Graves' disease from injections of pituitrin; Gottdenker [40] described an antagonism between pituitrin and the thyrotropic hormone; and Peczenik and Popper [41] reported that pituitrin prevents the thyroid hyperplasia due to anterior lobe hormone. Strauss [42] once observed clinical diabetes insipidus disappear with the onset of spontaneous myxedema.

In brief, then, the von Hann-Richter-Ranson theory holds that diabetes insipidus is due to hypopitressinemia in the presence of a diuretic hormone from the anterior pituitary. It is admittedly not a perfect hypothesis but no other has been proposed which harmonizes so many facts and against which there are so few objections. Some of the objections which have been raised are negative ones in the sense that they represent real gaps in our knowledge of pituitary physiology: e.g., the pars tuberalis is so closely adherent to the base of the brain as to make complete hypophysectomy to date an impossible achievement. Atwell [43] has attributed certain diuretic effects to extracts of the pars tuberalis but the function of this structure is virtually unknown. Similarly, it has been impossible to extirpate the pars intermedia alone or to remove the posterior lobe cleanly from it but Fisher's tissue assays [8] in experimental diabetes insipidus make it appear unlikely that this portion of the gland has anything to do with mammalian water metabolism.

On the positive side there are certain observations which prevent unqualified acceptance of the modern theory. It has been claimed [11, 44, 45, 46] that hypothalamic injury will produce diabetes insipidus in a previously hypophysectomized animal, a phenomenon which if true almost certainly eliminates hormonal participation. White and Heinbecker [30] have reviewed the evidence for this statement and conclude that it does not deserve complete support because the protocols lack adequate proof that anterior lobe tissue was absent or because the resulting polyurias were brief and possibly spontaneous. In view of such claims, however, it has been suggested that after hypophysectomy the tuber cinereum and hypothalamus vicariously assume the rôle of pituitrin manufacture [47] but the previously mentioned biological assays make this appear improbable,[8] and the impossibility of removing all of the tuberal and anterior lobe cells suggests that these post-

hypophysectomy punctures may have served only to stimulate production of diuretic material.

Again, if polyuria is due to the unrestrained diuretic effect of the anterior pituitary it is difficult to understand why extracts of this lobe do not induce diuresis in normal rats or increase the polyuria of hypophysectomized rats [48] and why implants of fresh tissue from the same source do not increase urine flow in hypophysectomized rats.[22]

Mahoney and Sheehan [23] found that diabetes insipidus could be produced by clipping the pituitary stalk in dogs but not in monkeys; they point out, however, that the monkey differs from the dog in that it is much easier to sever his stalk without hypothalamic injury than it is the dog's, that the nerve tracts in the stalk are more poorly developed, and that differences in blood supply probably account for the fact that stalk occlusion does not induce the same amount of posterior lobe atrophy that it does in dogs.

More recently Keller, Noble and Hamilton [49] reported that in five dogs they severed the stalk at its junction with the hypothalamus without injury to the anterior lobe, the pars intermedia or the hypothalamus and with minimal damage to the pars tuberalis; in several animals a slight increase in water consumption followed but none developed diabetes insipidus. Subsequent cauterization of the "proximal surface" of the separated gland induced marked polyuria, which soon disappeared in four dogs, and remained as a permanent diabetes insipidus in one. They also terminated a chronic hypothalamic polyuria by removal of the pituitary, an experiment reminiscent of Crowe, Cushing and Homans' early finding [50] that if anterior lobe tissue were immediately transplanted into hypophysectomized dogs polyuria continued until the transplant was removed.* The inconsistent feature of this report is the non-appearance of polyuria after denervation of the posterior lobe. The authors' description seems to indicate that, due perhaps to a more intact blood supply, there was less functional impairment of the separated gland than has usually occurred. This does not invalidate the conception that diabetes insipidus is in part due to hypopitressinemia but may indicate that destruction of the supraoptico-hypophyseal tract does not produce the same degree of posterior lobe insufficiency in the dog that it does in the cat.

Reference should also be made to the paradoxical capacity of certain subjects with diabetes insipidus to retain water [51] and salt.[52] The German school has long maintained that the disease is due to inability of the kidneys to concentrate electrolytes, a defect readily explainable by the hypopitressinemia theory, but it is less understandable why at least some individuals with diabetes insipidus should retain extra salt and water for long periods of time under conditions which should permit maximum excretion.[34]

Finally, and perhaps most puzzling of all, is the refractoriness of some diabetes insipidus subjects to pituitrin. Biggart's suggestion [53] that pituitrin

* In a subsequent paper [16] Cushing said that the same phenomenon accompanied transplantation and removal of posterior lobe tissue. So far as can be determined these conflicting observations have not been reconciled.

is effective only in the presence of intact hypothalamic nuclei apparently no longer holds, but the modern theory also offers no plausible explanation unless one is prepared to believe that diabetes insipidus can exist as the result of a chronic stimulus to diuresis arising in the pituitary.

So far as the thyroid is concerned, it is not clear why thyroidectomy abolishes the transient experimental polyurias and only partially inhibits the permanent ones. In any event, it is not thought that the thyroid plays more than a secondary rôle in clinical diabetes insipidus but it is hoped that the observations reported below show that its diuretic effect, limited as it is in humans, is not due solely to its capacity to accelerate cellular metabolism.

Case Report

W. D., a 55-year-old male negro, entered Barnes Hospital in the summer of 1936 complaining of polydipsia and polyuria of one year's duration. His previous health had been good, and the physical examination was unimportant except for moderate obesity and hypertension.

Laboratory Data: Blood count: erythrocytes 5,010,000, hemoglobin 105 per cent, leukocytes 6,400, eosinophiles 5 per cent, basophiles, myelocytes and juveniles 0 per cent, stabs 3 per cent, segmented 55 per cent, lymphocytes 33 per cent, monocytes 4 per cent. The urine was normal but on an unrestricted ward diet each 24 hour output averaged about 10 liters with a usual specific gravity of 1.002. Blood Kahn reaction, 4 plus. Lumbar puncture yielded a clear fluid under normal pressure containing 4–6 lymphocytes per cu. mm., a 2 plus Wassermann reaction, a colloidal gold curve of 2545555500, and protein content of 110 mg. per cent but a negative Pandy. Basal metabolic rate, minus 16 per cent. Plasma cholesterol 292 mg. per cent. Visual fields and roentgen-ray of the pituitary region negative.

Methods: The patient was placed on a diet containing less than 2 gm. of sodium chloride daily; extra salt was given him in a weighed shaker and the daily intake calculated by assuming that the diet contained 2 gm. and adding to this whatever salt was not returned in the shaker. It is believed that the recorded figures are accurate to less than 1 gm. daily. He was allowed to eat as much as he wished but the actual daily intake of protein, fat and carbohydrate was carefully weighed.* He usually consumed about 75 gm. of protein and 2000 calories daily.

Total thyroidectomy was performed by Dr. Peter Heinbecker on August 1, 1936.[54] Figure 1 is a section from the removed gland. The extreme resting phase may perhaps be correlated with the basal metabolic rate of minus 16 per cent but it is interesting to note that the pathologist on his initial report remarked that the appearance was not unlike that of thyroids from hypophysectomized animals.

Chart 1 depicts the water and sodium chloride output before and after thyroidectomy; the postoperative figures were obtained after the basal metabolic rate had fallen to an apparently constant low level of minus 35 to 40 per cent and the plasma cholesterol had risen to 490 mg. per cent. Unfortunately urinary nitrogen was not determined until the day of operation. Comparison of periods 1 and 6 when the diet contained an excess of salt shows that the average daily urine output had fallen by about 2 liters, a result similar to the finding of Fisher and Ingram [5] that thyroidectomy diminished the diuretic effect of sodium chloride in cats with experimental diabetes insipidus. Periods 2 and 7 show an increased response to pitressin after operation although the figures are not strictly comparable because of the greater salt intake during the preoperative interval. In periods 3 and 8, when the salt intake had been re-

*I am heavily indebted to Miss Isabel Grasser for her meticulous supervision of the diets.

duced to 5 gm. daily, it is seen that the average urine output in the two periods is practically identical, leading to the conclusion that in this instance thyroidectomy was no more effectively antidiuretic than a low salt diet. Periods 4 and 9 are believed to be comparable and again show that after operation the patient's sensitivity to pitressin was appreciably increased. Stern and Gilligan [55] had found that individuals with artificial myxedema were no more sensitive to pituitrin than normals. In period 5 desiccated thyroid in doses sufficient to raise the basal metabolic rate from minus 16 per cent to plus 7 per cent did not augment urine flow. Certain of the following observations suggest that the anticipated diuretic response did not occur because the

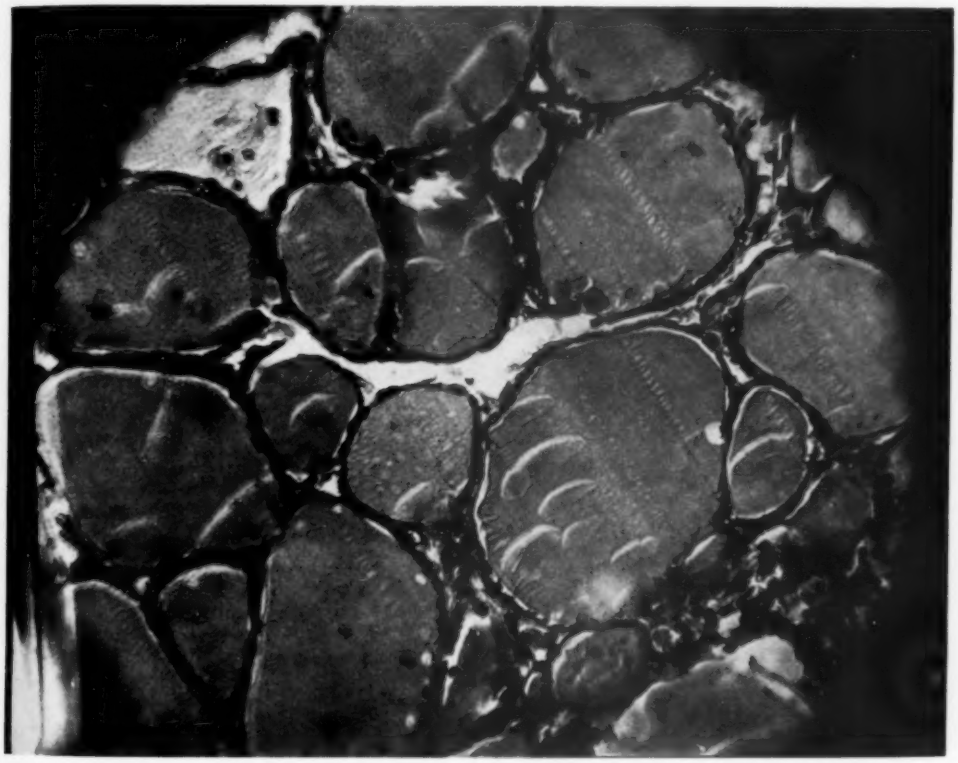

FIG. 1. High-power view of ablated thyroid.

patient was on a restricted salt intake. The postoperative nitrogen figures indicate increased protein storage.

As stated above, it has not been possible to decide whether the stimulating effect of thyroid upon water excretion is simply one expression of a general increase in metabolic processes or whether it is due to some more specific mechanism. Believing that information bearing on this point might be obtained by raising the postoperative basal metabolic rate to its former level with thyroid and again with some dissimilar agent under conditions which should permit maximum urine flow, the patient was placed on a generous salt intake and first given enough dinitrophenol to elevate the metabolic rate to about the preoperative level. Chart 2 shows the daily urine output and nitrogen balance under these circumstances and under subsequent thyroid administration. Dinitrophenol for five days promptly raised the basal metabolic rate to

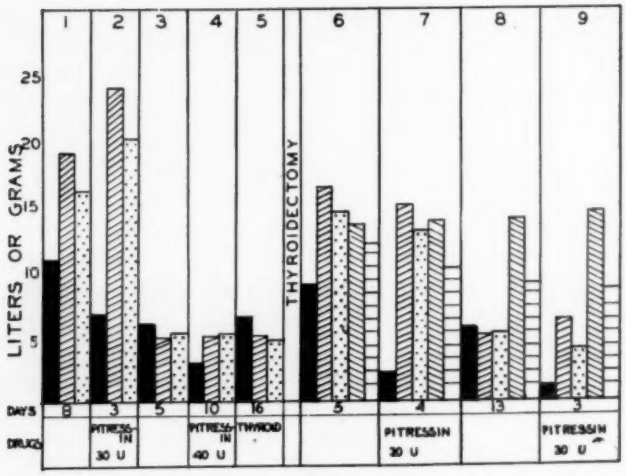

CHART 1. The columns in each period are the averages for the number of days indicated below.

—24 hour urine output.
—sodium chloride intake.
—sodium chloride output.
—nitrogen intake.
—nitrogen output.

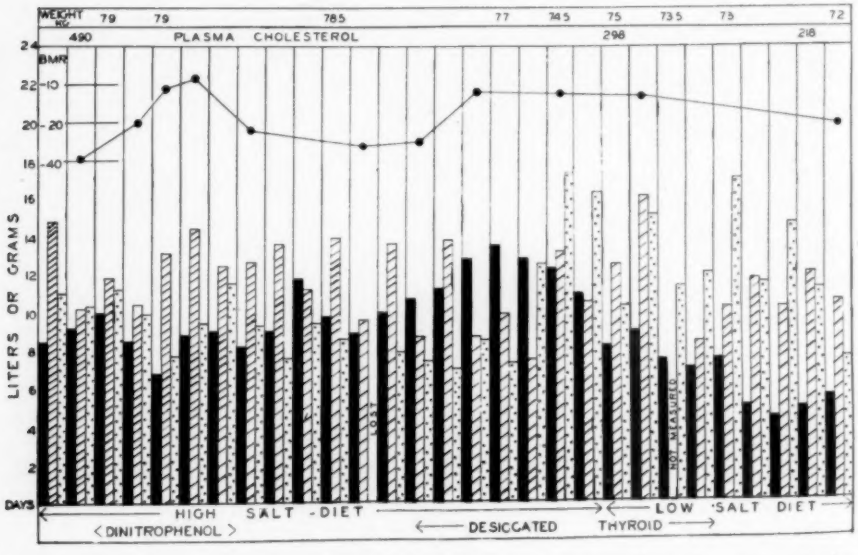

CHART 2. Effect of dinitrophenol and of thyroid upon the excretion of water and nitrogen in diabetes insipidus. Each group of 3 columns represents one day.

—urine output.
—nitrogen intake.
—nitrogen output.

minus 10 per cent but no diuresis occurred, the nitrogen balance remained virtually unchanged and there was no appreciable loss of weight. After the metabolic rate had fallen the procedure was repeated with thyroid and, so long as the high salt diet was continued, there was an unmistakable increase in urine volume; withdrawal of extra salt diminished this diuresis despite continuance of thyroid but did not abolish it. The nitrogen balance became strongly negative, plasma cholesterol dropped and the patient lost weight rapidly. These findings confirm the statement [56] that the rate of protein oxidation is not increased by dinitrophenol and indicate that the diuretic activity of thyroid is not wholly explained by the general increase in tissue metabolism. Heinbecker and White [15] in one dog in which thyroidectomy had diminished a chronic polyuria produced by hypothalamic puncture, also found urine flow increased by thyroid feeding but not by dinitrocresol.

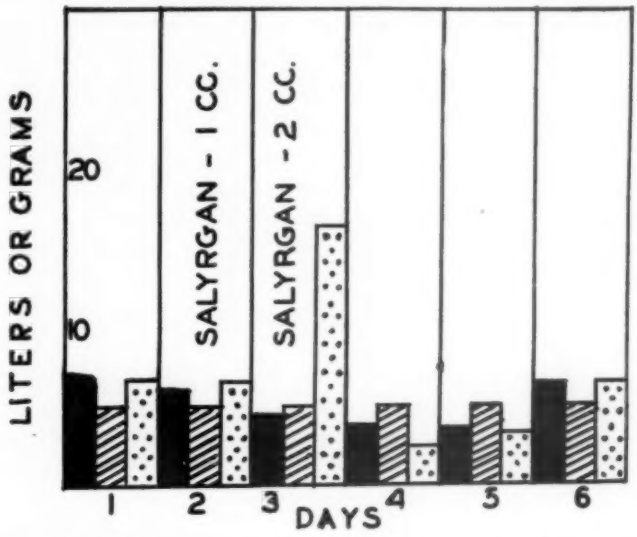

CHART 3. Effect of salyrgan on chloride excretion in diabetes insipidus.

—urine volume.
—sodium chloride intake.
—sodium chloride output.

Chart 3 shows that the chloride output may be increased by salyrgan in diabetes insipidus as in normals, a point of some interest in view of the emphasis placed by some [52] upon the constant hypotonicity of the urine in diabetes insipidus as an etiological factor. This observation was made preoperatively.

It may be incidentally remarked that in the preoperative period also we were unable to effect a greater reduction in urine volume by the combined use of pitressin and 1.8 gm. of amidopyrine daily than by pitressin alone. Postoperatively the patient was given 100,000 international units of Progynon-B daily for one week in a theoretical attempt to produce oliguria by inhibition of the anterior pituitary, but without demonstrable result.

By December 1936, four months after thyroidectomy, a definite hypochromic anemia had developed: erythrocytes 4,460,000, hemoglobin 78 per cent, leukocytes 10,200, eosinophiles 3 per cent, basophiles, myelocytes and juveniles 0, stabs 7 per

cent, segmenteds 53 per cent, lymphocytes 30 per cent, monocytes 7 per cent. The electrocardiogram indicated progressive myocardial damage but the characteristic changes of myxedema had not developed. The patient's general appearance and behavior had not changed and it is only fair to state that he regarded himself as definitely improved by the operation. The non-protein nitrogen of the blood had not departed significantly from its normal preoperative level.

Comment

This report is not intended as a rigidly controlled experiment in human physiology. Obviously no guarantee can be made that all thyroid tissue was removed although the drop in basal metabolic rate and the rise in blood cholesterol indicates that the operation was as thoroughly performed as could be expected. It is poor therapeusis to substitute one disease for another and we are not inclined to repeat the procedure. The patient's subjective satisfaction, his increased response to pitressin and his ability to tolerate larger quantities of salt without commensurate polyuria suggest that the operation might be of some benefit to pitressin-resistant individuals in view of the theoretical possibility that this type is due rather to overactivity of the anterior pituitary than to hypopitressinemia.

In the absence of microscopic proof of absent thyroid tissue we cannot, however, claim that thyroidectomy in humans is less effective in reducing the polyuria of diabetes insipidus than it is in the experimental disorder of cats and dogs. That the thyroid exerts an appreciable effect on water exchange has been demonstrated and it is believed that this comes about either through its ability to sensitize the organism to a specific diuretic principle from the anterior pituitary or through a specific diuretic activity of its own.

Summary

1. Current views regarding the etiology of diabetes insipidus are presented and the secondary rôle of thyroid activity assessed.

2. The changes in water, sodium chloride and nitrogen metabolism induced by total thyroidectomy in a human with diabetes insipidus are described. Although ablation of the thyroid was no more effective in reducing urine output than a low salt diet it definitely increased the patient's reactivity to pitressin and diminished his diuretic response to sodium chloride.

3. Comparison of the urine volume response to dinitrophenol and to desiccated thyroid suggests that the diuretic activity of thyroid is not due solely to its ability to elevate the metabolic rate.

4. Under the influence of salyrgan the kidneys of an individual with diabetes insipidus eliminated urine rich in chloride. Therefore, if diabetes insipidus is primarily due to inability of the kidneys to concentrate urine, the defect is not irreversible.

Addendum

Since this was written several pertinent papers have appeared. Keller and Hamilton [57] oppose the Ranson school in reporting that complete denervation of the

posterior pituitary of cats does not always result in diabetes insipidus; they evidently place more emphasis upon their negative results than upon their successes. Keller [58] induced chronic polyuria in a dog by hypothalamic puncture, abolished it by hypophysectomy, and then reëstablished it first by anterior lobe injections and again by thyroid feeding. He too feels that anterior lobe is necessary for the existence of diabetes insipidus but apparently believes that the diuretic and thyrotropic hormones are identical. McConnell [59] has reported striking amelioration of diabetes insipidus in a woman by removal of a thyroid adenoma; the fact that her polyuria was said to be uninfluenced by pituitrin in any form intensifies our desire to repeat these observations on pitressin-resistant individuals. Cutler's results from thyroidectomy were apparently not striking.[60]

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SUBACUTE BACTERIAL ENDOCARDITIS: ACTIVE CASES WITHOUT BACTEREMIA *

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For several years I have been interested in the group of patients with active bacterial endocarditis without bacteremia during life. These cases are not infrequent, and since organisms can be isolated from the vegetations post mortem, it is a matter of some interest to gather more information regarding the nature of the local lesion in the valves and the mechanism concerned with the absence of bacteremia.

The relative incidence of these so-called " bacteria free " † [1] cases varies in the experience of different observers. In the last 54 cases of endocarditis which came to necropsy at the Boston City Hospital,‡ the blood cultures and the heart's blood cultures at postmortem examination were negative in 13 or 24 per cent of the cases. In all of these the organisms were cultured from the vegetations and found by microscopic examination of the heart valves. Other observers report that in anywhere from 15 to 25 per cent of the cases which are observed, bacteremia cannot be shown to be present.

At this time, I present a summary of 15 cases which I have observed during life and at post mortem, including the clinical features, the histologic picture of the valves, and some observations regarding the bactericidal activity of the blood in patients with bacterial endocarditis.

Analysis of Cases

Of the 15 cases, all showed fever at some time during the course of the disease which lasted from six weeks to 12 months. Ten of the patients were between 21 and 40 years of age, one was under 20, and four were between 41 and 50 years. Seven gave a history of previous attacks of rheumatic fever occurring from one to 36 years before the onset of symptoms suggesting bacterial endocarditis. In two, there were congenital bicuspid aortic valves. All of the patients had heart murmurs. The aortic valve was involved alone in seven instances, and in combination with a mitral valvular defect in three. The mitral valve was involved alone in two cases, and the tricuspid alone in three. All of the individuals had an anemia.

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† The term "bacteria free" cases was first introduced by Libman.[2] Sometimes it refers to cases without bacteremia but with organisms in the heart valves. In other instances, the term has been further restricted to those cases in which one can not obtain bacteria from the heart valves at necropsy (healing or healed bacterial endocarditis).

‡ I am indebted to Dr. Parker, Director of the Mallory Institute of Pathology, for allowing me to use the records for this information. He has also been very generous in studying the sections of the heart valves with me.

Emboli were present in the lungs in all of the cases with right-sided valvular defects. The brain, spleen, kidneys, and extremities were the favorite sites for emboli in the peripheral circulation. A mycotic aneurysm of the superior mesenteric artery was found in one case and small infarcts of the intestine with melena in two. The heart's blood culture was negative at post mortem in all, except two that showed a terminal invasion by bacteria: one a Friedlander bacillus sepsis, the other a hemolytic streptococcus sepsis. In all cases organisms were cultured from the heart valves.

For purposes of discussion it is convenient to divide the cases into groups according to their outstanding clinical features during the course of the disease. I have separated the present cases into those with: (1) right-sided heart lesions and multiple pulmonary infarcts; (2) symptoms and signs of progressive renal insufficiency; (3) progressive heart failure; (4) hemiplegia, as the outstanding feature; (5) splenomegaly and anemia. The salient features are presented in table 1.

Cases with Right-Sided Valvular Lesions. The only conspicuous features of these cases which were not present in the others were the signs of multiple pulmonary infarcts and jaundice. Embolism in the general circulation was lacking but acute diffuse (non-embolic) nephritis was present in all. It has been pointed out in the past by Blumgart [3] and others that right-sided bacterial endocarditis may be associated with multiple pulmonary infarcts without bacteremia, and it has been postulated that one of the reasons for the absence of bacteremia is due to the clearing capacity of the lungs. This is undoubtedly a factor but it can not be the only explanation since a number of patients with bacterial endocarditis and infections confined to the right side of the heart have bacteremia.[4] Of considerable interest in these cases is the presence of non-embolic nephritis, a feature of considerable importance in diagnosis. The splenomegaly that occurs is due to an acute splenic tumor, and the jaundice which usually appears late in the course of the disease is probably due to excessive blood destruction, chronic passive congestion of the liver, and the anoxemia following multiple pulmonary infarctions. The following case is an example.

Case 1. A young man, 34 years of age, entered the hospital complaining of cough and frequent attacks of vomiting. His past and family histories were negative. He had always been well until three months ago, when he noticed shortness of breath and paroxysmal attacks of coughing with some blood-streaked expectoration. There was, in addition, some aching pain in the chest, exaggerated by respiratory effort though it was more or less continuous. There was also dull, aching precordial pain and frequent attacks of sweating at night. Three weeks before admission all of his symptoms became exaggerated and his feet began to swell. It became necessary for him to go to bed, and he had remained there for three weeks before he came to the hospital.

Physical examination showed a thin, undernourished young man. His temperature was 102° F.; pulse and respiratory rates were 120 and 40 per minute, respectively. The blood pressure was 150 mm. of Hg systolic and 70 mm. of Hg diastolic. There was moderate dyspnea but no orthopnea. The positive findings included: Signs of

TABLE I

Summary of 15 Cases of Bacterial Endocarditis Without Bacteremia

Case No., Age and Sex	Previous Rheumatic History	Signs of Infection	Signs of Valvular Disease	Embolic Phenomena	Heart Failure	Renal Disease	Blood Findings	Duration of Illness	Necropsy Findings	Miscellaneous Features
Patients with Right Sided Valvular Lesions										
1. 29 yrs. ♀	None	Chills and fever 101–104° F.	Systolic murmur over lower end of sternum	Signs of multiple pulmonary infarcts. Rales and pleural friction rub. None elsewhere	Slight peripheral edema and hepatomegaly	None. B.P. 125/80 mm. Hg.	R.B.C. 3,600,000–2,500,000 per cu. mm. Hgb. 57–35%. W.B.C. 5,600–13,600 per cu. mm.	6 weeks	Ulcerative endocarditis. Multiple pulmonary infarcts. *Streptococcus viridans* from heart valves. No signs of previous valve disease	Jaundice. Infection followed an abortion. 6 blood cultures during life were negative
2. 34 yrs. ♂	None	101–103° F.	Systolic and diastolic murmur over lower end of sternum	Signs of pulmonary infarction. Cough. Hemoptysis. Cyanosis. None elsewhere	Enlarged liver. Dyspnea. Slight peripheral edema	Urine showed: red blood cells, casts, albumin. B.P. 115/70 mm. Hg.	R.B.C. 2,952,000 per cu. mm. W.B.C. 32,400 per cu. mm.	3 months	Acute endocarditis, tricuspid valves (*Staphylococcus aureus*). Septic embolus in pulmonary artery—infarcts left lung—serofibrinous pleurisy. Acute glomerulonephritis. Ascites. Hydropericardium	Jaundice. 3 blood cultures during life were negative
3. 32 yrs. ♂	Pains in joints at age of 14 yrs.	99–100.4° F.	Systolic murmur at lower end of sternum	Signs of pulmonary infarct with cough. Pain and pleurisy	Dyspnea. Dependent edema	Urine showed: albumin, red blood cells, casts, and leukocytes. Sp. Gr. 1.016. B.P. 160/100 mm. Hg. Phthalein 20% 2 hrs. CO_2 28 vol. %. N.P.N. 48.8–96.8 mg. per 100 c.c.	R.B.C. 2,656,000 per cu. mm. Hgb. 42%	4 months	Tricuspid endocarditis (*Streptococcus viridans*). Chronic passive congestion of liver. Pulmonary infarct with empyema. Chronic glomerulonephritis. Terminal *B. Friedlander* bacteremia	Blood cultures negative until day before death; then *B. Friedlander*. Paroxysmal auricular fibrillation. Death from renal insufficiency.
Patients with Symptoms and Signs of Renal Insufficiency										
4. 48 yrs. ♂	None	No fever	Aortic insufficiency	None	Edema of legs. Dyspnea	Urine showed: albumin, red blood cells, white blood cells, casts. Sp. Gr. 1.012. N.P.N. 105 mg. per 100 c.c. B.P. 120/0 mm. Hg.	R.B.C. 3,350,000 per cu. mm. Hgb. 52%. W.B.C. 16,800 per cu. mm.	1 year	Vegetative endocarditis, congenital bicuspid valve (*Streptococcus viridans*). Focal embolic nephritis	Bicuspid aortic valve. Course characterized by progressive nephritis and heart failure.
5. 40 yrs. ♂	None	98–101° F.	Aortic insufficiency	Infarcts in spleen and kidneys	Edema of legs. Dyspnea	Urine showed: albumin, red blood cells, casts. Sp. Gr. 1.016. N.P.N. 30–106 mg. per 100 c.c. B.P. 150/60 mm. Hg.	R.B.C. 3,870,000 per cu. mm. Hgb. 60%. W.B.C. 11,000 to 15,000 per cu. mm.	6 months	Vegetative endocarditis, aortic valve. Infarcts of spleen and kidneys. Chronic diffuse glomerulonephritis	Clubbed fingers. 5 blood cultures negative. Splenomegaly
6. 45 yrs. ♂	None	99–100.5° F.	Systolic and diastolic murmur at apex and base	None	Edema of extremities	Urine showed: albumin, red blood cells, rare casts. Sp. Gr. 1.011–1.017. Phthalein 52% 2 hrs. B.P. 165/80 mm. Hg. N.P.N. 50 mg. per 100 c.c.	R.B.C. 3,440,000 to 2,125,000 per cu. mm. W.B.C. 10,000 to 13,000 per cu. mm.	1 year	Vegetative endocarditis, aortic and mitral valves (*Streptococcus viridans*). Healed infarcts in kidney and spleen. Chronic diffuse nephritis	
7. 30 yrs. ♂	8 years ago	No fever	Systolic murmur at apex	Infarct of intestine	Generalized edema	Urine showed: albumin, red blood cells, casts. Sp. Gr. 1.014. B.P. 160/100 mm. Hg. N.P.N. 80 mg. per 100 c.c. CO_2 21 vol. %	R.B.C. 2,392,000 per cu. mm. W.B.C. 15,200 per cu. mm. Hgb. 38%	8 months	Vegetative endocarditis, mitral valve and wall of auricle (*Streptococcus viridans*). Chronic diffuse nephritis. Infarct of jejunum	Splenomegaly. Melena. Diffuse petechial hemorrhages in skin

Summary of 15 Cases of Bacterial Endocarditis Without Bacteremia—*Continued*

Summary of 15 Cases of Bacterial Endocarditis Without Bacteremia—*Continued*

Case No., Age and Sex	Previous Rheumatic History	Signs of Infection	Signs of Valvular Disease	Embolic Phenomena	Heart Failure	Renal Disease	Blood Findings	Duration of Illness	Necropsy Findings	Miscellaneous Features
8. 25 yrs. ♀	1 year ago	100–101° F.	Systolic and diastolic murmur at apex	None	None	Urine showed: albumin, red blood cells, casts. Sp. Gr. 1.016–1.020. N.P.N. 50–60 mg. per 100 c.c. Phthalein 9% 2 hrs. B.P. 180/120 mm. Hg.	R.B.C. 4,300,000 per cu. mm. Hgb. 75%. W.B.C. 15,100 to 25,100 per cu. mm.	6 months	Vegetative endocarditis, mitral and aortic insufficiency. Diffuse nephritis. Bronchopneumonia	
9. 38 yrs. ♀	18 years ago	Slight fever for 1 week 100–101° F.	Systolic murmur at apex	None	Dyspnea Edema	Urine showed: albumin, red blood cells, white blood cells. N.P.N. 80–120 mg. per 100 c.c. B.P. 160/70 mm. Hg. Sp. Gr. 1.011–1.013	R.B.C. 1,700,000 to 2,000,000 per cu. mm. W.B.C. 4,950 to 10,050 per cu. mm. Hgb. 30–35%	4 months	Bacterial endocarditis, mitral and aortic valves (*Streptococcus viridans*). Acute embolic glomerulonephritis	
Patients with Symptoms and Signs of Cardiac Insufficiency										
10. 48 yrs. ♂	36 years ago	99–100° F.	Systolic and diastolic murmur at apex and base	Petechial hemorrhages	Dyspnea Palpitation Edema	Urine showed: albumin and casts. Sp. Gr. 1.028 to 1.030. N.P.N. 30 mg. per 100 c.c. B.P. 140/30 mm. Hg.	R.B.C. 3,300,000. Hgb. 72–52%. W.B.C. 3,500 to 8,600 per cu. mm.	6 months	Vegetative endocarditis on mitral and aortic valves (*Streptococcus viridans*)	Clubbed fingers. 11 blood cultures were negative. Edema progressive
11. 43 yrs. ♂	None	99–102° F.	Aortic insufficiency	None	Edema Dyspnea	Urine showed: albumin, red blood cells, white blood cells, and casts. Phthalein 55% 2 hrs. N.P.N. 32–40 mg. per 100 c.c. B.P. 130/20 mm. Hg.	R.B.C. 2,730,000 per cu. mm. Hgb. 55%. W.B.C. 15,200 per cu. mm.	11 months	Vegetative endocarditis, aortic valve. Anasarca. Cirrhosis of liver	Bicuspid aortic valve. Splenomegaly. 25 blood cultures were negative
12. 30 yrs. ♂	None	98.6–100.6° F.	Aortic insufficiency	Hemiplegia	Dyspnea Orthopnea Edema	Urine showed: albumin and red blood cells. Sp. Gr. 1.020. N.P.N. 33 mg. per 100 c.c. B.P. 140/20 mm. Hg.	R.B.C. 3,060,000 per cu. mm. Hgb. 54%. W.B.C. 7,300 per cu. mm.	6 months	Vegetative endocarditis of aortic valve with rupture (*Streptococcus viridans*)	
Patients with Symptoms and Signs of Cerebral Embolism										
13. 37 yrs. ♂	None	100.8–102° F.	Aortic insufficiency	Hemiplegia Renal infarcts	Dyspnea Edema of extremities	Urine showed: Sp. Gr. 1.024, albumin, red blood cells, white blood cells, and casts. N.P.N. 42–80 mg. per 100 c.c. P.S.P. 39% 2 hrs. B.P. 110/50 mm. Hg.	R.B.C. 4,340,000 per cu. mm. Hgb. 70%. W.B.C. 18,000 per cu. mm.	7 months	Vegetative endocarditis, aortic valve (*Streptococcus viridans*)	12 blood cultures negative. Terminal hemolytic streptococcal bacteremia
14. 22 yrs. ♂	9 years ago	99–103° F.	Aortic insufficiency	Hemiplegia. Petechial hemorrhages	None	Urine showed: albumin, red blood cells. B.P. 110/70 mm. Hg.	R.B.C. 4,100,000 Hgb. 84–57%. W.B.C. 11,500 to 19,400 per cu. mm.	6 weeks	Vegetative endocarditis, mitral and aortic valves (*N. Pharyngis sicca*). Infarcts in spleen—kidney	Splenomegaly. 8 blood cultures negative
Patient with Splenomegaly and Anemia										
15. 14 yrs. ♀	10 years ago	101–102° F.	Mitral and aortic insufficiency	Left lower extremity	Dyspnea Edema	Urine showed: albumin, red blood cells, white blood cells, and casts. N.P.N. 21 mg. per 100 c.c. B.P. 110/70 mm. Hg.	R.B.C. 2,100,000 per cu. mm. Hgb. 40–43%. W.B.C. 6,800 to 25,100 per cu. mm.	6 months	Vegetative endocarditis of mitral and auricular wall	Splenomegaly, spleen reaching to umbilicus

solidification of the lung over the right lower lobe and a fibrinous pleurisy, moderate distention of the abdomen, an enlarged liver, and edema of the legs. The heart was moderately enlarged and there was a to-and-fro murmur over the precordium with systolic accentuation, which was best heard over the tricuspid area. The murmur was well localized and was not transmitted to the axilla.

Laboratory examination showed a red blood cell count of 2,952,000 per cubic millimeter, hemoglobin of 58 per cent, and a white blood count of 32,400 per cubic millimeter. Blood Wassermann was negative. The urine showed albumin and a moderate number of casts and red blood cells. The blood culture on admission was negative. There was no clubbing of the fingers.

The course of his illness was characterized by irregular fever, varying from 100° to 103° F. The pulse rate varied from 100 to 130, and the respiratory rate from 28 to 36 per minute. The spleen was not palpable. There were no petechial hemorrhages observed and no signs of peripheral embolism to the extremities. Four blood cultures during the course of a month were all negative. He continued to complain of recurrent attacks of pain in the chest, and signs of fluid appeared in both pleural cavities. Cyanosis became a feature of the illness. Finally, four days before death, the skin and sclerae had a definite icteric tint and the urine contained bile pigment. He failed gradually and died one month after admission, the total duration of the illness from the onset of symptoms being four months.

The necropsy showed: endocarditis of the tricuspid valves, septic emboli in the pulmonary artery, with infarcts in the lung, sero-fibrinous pleurisy, acute diffuse glomerulonephritis, and a small encapsulated empyema between the lobes of the right lung. There was a moderate hydropericardium and ascites.

In short, then, this was a young man who had the symptoms and signs of an acute infection with fever, tachycardia, increased respiratory rate, signs of myocardial insufficiency, an enlarged liver, edema of the extremities, a systolic murmur over the precordium, a friction rub over the lungs, hematuria, jaundice, repeated negative blood cultures, and a progressive anemia with leukocytosis. The clinical features of the case suggested a right-sided valvular disease with multiple pulmonary infarcts and an acute, diffuse glomerulonephritis.

To sum up, in these cases the symptoms and signs of infection, the signs of right-sided valvular disease (tricuspid or pulmonary insufficiency), multiple pulmonary infarcts without signs of emboli in the greater circulation, with or without the signs of nephritis, and the late appearance of jaundice are the outstanding clinical features. Hemoptysis may be a feature in these patients and results from either pulmonary infarcts or mycotic aneurysms of the pulmonary vessels. These characteristics are highly suggestive of a bacterial infection localized on the right side of the heart.

Cases with Renal Insufficiency. One of the most frequent signs of bacterial endocarditis with bacteremia is a focal embolic glomerulonephritis. In most instances, there are indications from the examination of the urine, such as hematuria, which suggest embolic lesions. In a few cases with bacteremia, the renal damage is so great that definite signs of renal insufficiency command attention, and one may find nitrogen retention, acidosis, and moderate hypertension.

In some of the cases with negative blood cultures during life and active lesions in the endocardium from which bacteria can be isolated, progressive renal insufficiency is a conspicuous feature. In the present group, focal embolic lesions were found in eight cases, and in the remaining seven the process was that of a diffuse glomerulonephritis.

In seven cases there were conspicuous signs of renal insufficiency as manifested by albuminuria, hematuria, loss of concentrating power, nitrogen retention, acidosis, and moderate hypertension. The most important features of these cases are the signs of progressive renal failure in an individual with valvular heart disease, with the symptoms and signs of a chronic infection and embolic phenomenon. The following case is an example.

Case 2. A 45 year old man complained of swelling of the face and feet. His family and past histories were negative. He stated that he had always been quite well until one month before admission to the hospital when he began to notice shortness of breath on slight exertion. His shoes became tight, especially at night, and his face and scrotum were swollen. In addition, he noted that his urine was somewhat cloudy and dark red in color. He became increasingly thirsty and passed more urine than formerly. His sleep was disturbed on account of nocturia. He had been in bed for one week before admission to the hospital. He had lost weight and his appetite had become progressively less.

Physical examination showed a well nourished and developed man who was alert and coöperative. His temperature was 101° F., pulse rate 80 per minute, and respirations varied between 20 and 25 per minute. The heart was enlarged to the left, measuring 14 cm. in the sixth interspace and extending 3 cm. to the right of the midsternal line in the fourth interspace. There was a harsh systolic murmur at the apex and base, and a soft blowing diastolic murmur in the aortic area. Lungs were clear. Blood pressure was 165 mm. of Hg systolic and 80 mm. of Hg diastolic. The abdomen was negative and there was slight edema of the ankles.

Laboratory examination showed a red blood count of 3,440,000 per cubic millimeter, hemoglobin of 55 per cent, and a white blood count of 14,800 per cubic millimeter. Specific gravity of the urine varied from 1.011 to 1.017. There was a slight trace of albumin, rare red blood cells and white blood cells, and no casts. Phenolsulphonphthalein excretion was 42 per cent in 2 hours.

After a period of several months in the hospital he improved, as far as his edema and symptoms were concerned, but the albuminuria persisted. The red blood cells had disappeared from the urine. He was discharged and returned six months later, complaining of increasing edema, slight dyspnea, nocturia, and loss of weight.

Physical examination at that time showed that he was dyspneic and cyanotic. He had râles at both lung bases and signs of aortic and mitral regurgitation. The liver was moderately enlarged and there was tenderness over it. There was extensive edema of the legs and scrotum.

Laboratory examination showed that the specific gravity of the urine varied from 1.010 to 1.015. Urine contained large amounts of albumin, many hyaline and granular casts, and a few red blood cells and white blood cells. The red blood cell count was 2,940,000 per cubic millimeter; the white blood cell count was 13,000 with a differential count of 75 per cent polymorphonuclears. Electrocardiographic examination indicated nothing abnormal. Blood pressure was 125 mm. of Hg systolic and 52 mm. of Hg diastolic. Temperature ranged between 99° and 100.5°. Non-protein nitrogen was 50 mg. per 100 c.c., gradually increasing to 65 mg. per 100 c.c. Phenolsulphonphthalein excretion was 5 per cent in two hours. Nitrogen retention, progressive anemia, and death followed 10 months after the onset of symptoms.

Necropsy showed: Vegetations on the mitral and aortic valves. Heart's blood culture was negative. Streptococci of the viridans type were cultured from the heart valve. There was acute and chronic glomerulonephritis and a few focal embolic lesions, but the conspicuous feature was diffuse glomerulonephritis without embolization.

In summary, then, this man had the symptoms and signs of cardiac and renal insufficiency, with valvular heart disease, low-grade fever, negative blood cultures, and a progressive nephritis, death occurring with renal insufficiency.

Comment. The renal lesions that are encountered in bacterial endocarditis have been studied especially in this country by Baehr and his associates.[5, 6] From Baehr's most recent study a number of important facts emerged. In a series of 91 cases of subacute bacterial endocarditis with bacteremia, the kidneys showed embolic lesions in 84 and were normal in five. In two there was a diffuse glomerulonephritis; in one, it was acute and in the other the process was a chronic one. A terminal azotemia was present in six.

In the 57 patients in the "bacteria free" stage the situation was somewhat different. It is well at this point to say that Baehr defines the "bacteria free" cases as those showing persistently negative blood cultures during life and no bacteria in the vegetations at post mortem when they were examined. In these cases he found evidence of healed focal embolic lesions in 34 and glomerulonephritis in 19, or 33.3 per cent.

In short, then, Baehr points out that patients with bacteremia show focal embolic lesions very often and diffuse glomerulonephritis infrequently. In the "bacteria free" cases diffuse glomerulonephritis is more common and the focal glomerular lesions usually show signs of healing.

It is perhaps well worth noting and emphasizing, then, that diffuse glomerular nephritis appears to be a striking feature in the cases without bacteremia. Rich, Bumstead, and Frobisher[7] have produced nephritis in animals with hemorrhage into the capsules and tubules by injecting bacteria-free filtrates of broth cultures of organisms derived from bacterial endocarditis. From numerous observations at necropsy and from their experimental work, they expressed the opinion that the circulating bacteria and their products were responsible for the nephritis of bacterial endocarditis rather than focal embolic lesions. To account for the varying frequency of glomerular nephritis in patients with subacute bacterial endocarditis, Rich, Bumstead and Frobisher offer the suggestion that the difference may be accounted for by variations in the strain of infecting organism. Baehr has likewise suggested that the presence of streptococci in the blood can not be the sole cause of the glomerular nephritis inasmuch as it is seen most often in cases without bacteremia. It was suggested that the glomerular nephritis was related to the phenomena concerned in or following the death of the bacteria. In brief, one group of investigators feels that differences in the infecting strain of bacteria are of importance, whereas others postulate differences in the immune mechanism of the disease in various indi-

viduals. Whatever the final explanation may be, it is well to consider bacterial infection of the heart valves as a cause of glomerulonephritis, and it is also important to appreciate that it is most common in cases without bacteremia.

Cases with Cardiac Insufficiency. As a late phenomenon, many patients with active bacterial endocarditis and bacteremia develop all of the symptoms and signs of congestive heart failure. In these, the symptoms and signs of infection invariably precede those of heart failure. A few of the patients with negative blood cultures came under observation with the symptoms of cardiac insufficiency which dominated the illness from the beginning of symptoms. The following case is an example.

Case 3. A 48 year old man complained of palpitation and dyspnea of three months' duration. He had had an attack of rheumatic fever at the age of 12 years but no symptoms referable to his heart and no pains in his joints until three months before admission. At that time he began to notice dyspnea, palpitation, and slight edema of the extremities, especially at night. On occasions, he had attacks of paroxysmal dyspnea which would awaken him from sleep and cause him to gasp for breath. For one month before admission he had had recurrent chills and fever, followed by sweating, progressive weakness, chronic cough, and some pain in the left upper quadrant radiating to his chest and abdomen. His past history was essentially negative except for the attack of rheumatic fever. Family history was inconsequential.

Physical examination showed a poorly developed and nourished man with dyspnea and the appearance of being acutely ill. His temperature was 99.5° F.; pulse and respiratory rate were 100 and 22 per minute, respectively. Blood pressure was 100 mm. of Hg systolic and 48 mm. of Hg diastolic. Positive findings were: Moderate enlargement of the heart to the left, a blowing systolic murmur at the apex, and a systolic and diastolic murmur at the aortic area. There were râles at both lung bases. The abdomen was moderately distended but no free fluid was detected. There was slight edema of the extremities and moderate clubbing of the fingers.

Laboratory examination showed that the specific gravity of the urine varied from 1.010 to 1.028. There were rare red blood cells and, on occasions, numerous casts. The red blood cell count was 3,300,000 per cubic millimeter, hemoglobin 72 per cent, and the white blood cell count 3,500 to 8,600 per cubic millimeter. The differential count was normal. Sedimentation rate was increased. Electrocardiographic examination showed a P–R interval of 0.16 sec. and left ventricular preponderance. Fluoroscopic examination of the heart showed a dilated pulmonary artery. Blood culture was negative.

The patient was observed for a period of three months. During that time he had low-grade fever, ranging from 99.5° to 100° F. He complained of pains in his joints which were controlled to some extent by the administration of sodium salicylate. The edema which was present on admission gradually subsided but he continued to have râles in both lungs and attacks of paroxysmal dyspnea. The spleen was not felt at any time. On a few occasions a few petechial hemorrhages were observed on the lip, the buccal mucosa, and over the arms and chest. The course of the patient's illness was one of progressive failure with the predominating symptoms those of cardiac insufficiency, such as dyspnea, restlessness, and moderate edema of the extremities. There was a progressive anemia, the hemoglobin declining to 55 per cent, without any response to iron or liver extract therapy. Eleven blood cultures taken over a period of three months of observation were all negative.

At necropsy, the heart's blood culture was negative. The anatomical diagnoses were: Healed rheumatic aortic endocarditis, vegetative endocarditis of the aortic

valves. Culture of these vegetations revealed *Streptococcus viridans*. There was chronic passive congestion of the liver and spleen, a few infarcts in the spleen, and a few focal embolic lesions in the kidney.

In brief, then, a patient who had had rheumatic fever at the age of 12 years, develops the symptoms of cardiac insufficiency six months before death. The clinical course during the last three months of his life was characterized by progressive cardiac insufficiency, the signs of a low-grade infection (slight fever, loss of weight, and a progressive anemia), aortic insufficiency, clubbed fingers, petechial hemorrhages in the skin, and persistently negative blood cultures, death resulting from cardiac insufficiency. The heart at postmortem examination showed vegetative endocarditis of the aortic valves from which *Streptococcus viridans* were isolated. The section of heart valve is shown in figure 1.

FIG. 1. Vegetation on aortic valve. The deeply staining material at the periphery of the valve is a mass of bacteria.

There were two cases in which hemiplegia was the first indication of bacterial endocarditis, and a third in which splenomegaly was an outstanding feature. They have been summarized in the table.

Differential Diagnosis

The conditions which are likely to be confused with infective endocarditis without bacteremia are active and progressive rheumatic infections and the cases of non-bacterial thrombotic endocarditis.[8, 9, 10] The absence of embolic phenomena, splenomegaly, and nephritis and the presence of electrocardiographic changes and pericarditis favors the diagnosis of rheumatic fever. The history of rheumatic fever and a positive nucleoprotein skin reaction is also of assistance.

The cases of non-bacterial thrombotic endocarditis may give rise to greater difficulty in that they may show clinical features which are common to either rheumatic fever or infective endocarditis, in that they may have pericarditis, polyserositis, nephritis, and skin eruptions of lupus erythematosis, but no electrocardiographic changes. Thrombopenic purpura hemorrhagica and deforming arthritis may be features. All these features, together with the course of the disease, are helpful in the diagnosis.

Lesions in the Heart Valves

In view of the observation that the blood remained sterile in these cases it was of some interest to study the heart valves and vegetations from which organisms were grown at post mortem and compare the finding with cases showing bacteremia.

Histologic Changes in Heart Valves. When the sections from the heart valves showing vegetations were studied with the microscope for purposes of comparing the lesions in the cases without bacteremia with those with bacteremia, it was found that it was impossible to distinguish the cases on this basis. Some of the vegetations showed organization and fibrosis, others from the same valve would exhibit no signs of healing. Morphologically, the organisms appeared to be the same although careful studies for differences in their growth characteristics were not investigated.

The sequence of events in the development and advance of the lesions seems to be somewhat as follows. There is an injury or damage to the endothelium of the valvular surface, which is followed by the formation of platelet and fibrinous thrombi, proliferation of the fibroblasts, and endothelial cells. The infecting vegetations are usually superficial, covering the surface of the valve and consisting of masses of fibrin and platelets. The organisms frequently collect and arrange themselves along the border of the vegetations, and beneath them in some cases one sometimes sees masses of leukocytes. In other vegetations it can be seen that the dense clumps of bacteria at the periphery of the thickened layer of fibroblasts are surrounded by a wall of leukocytes and fibrin.

When the vegetations organize, one finds a gradual transformation of the fibroblastic layer into dense connective tissue. The vegetations themselves are covered with dense fibrin and deeply stained material and it appears as

if the vegetations were being completely surrounded by fibrous tissue, and shut off from the circulating blood.

The histologic findings in these cases are in accord with those described by Wright [1] who could find no difference in the vegetations from cases with and without bacteremia.

It does not seem that one can account for the absence of bacteremia in these cases solely on a basis of the difference in the anatomic structure of the vegetations on the heart valves. While it can not be proved at present, there is suggestive evidence from animal experimentation that the cases with negative blood cultures probably have a sufficiently high bactericidal power of the blood to maintain the clearing mechanism at a high level of efficiency. The other possibility is that the organisms are growing so slowly that they can be removed as fast as they enter the circulating blood. That they enter the circulating blood from the vegetations is supported by the fact that patients with negative blood cultures often have emboli in the various organs which contain bacteria.

Comment

It can not be said that the cases without bacteremia differ essentially from those with bacteremia during life, insofar as their clinical features and course are concerned. The total duration of the illness may be the same in both groups, and there may be no distinguishing marks by which they can be separated during life. There is possibly one exception which is noticeable, and that is the incidence of renal insufficiency in the cases without bacteremia. This question has been discussed above and need not be repeated here. No one will deny, however, that renal failure may be observed in cases with bacteremia even though it seems to be less common than in those without bacteremia during life.

Inasmuch as there is difficulty in distinguishing these two groups of patients on a basis of the clinical features and course of the disease, it will be well to review a number of the salient features and facts regarding the pathogenesis of bacterial endocarditis in man and in the experimental animal. In this way, we seek an explanation for the cases under discussion.

The Pathogenesis of Bacterial Endocarditis in Man

In reviewing the conditions in which subacute bacterial endocarditis is seen in man, certain points stand out. First of all, it is generally conceded that it is most commonly observed in individuals who have damaged valves resulting from a previous attack of rheumatic fever or from congenital valvular defects. It is rare when the preceding rheumatic infection has been an attack of chorea.[11] In particular, it seems to be especially common in patients who have chronic valvular heart disease and a regular rhythm; of these, the ones who seem to be most vulnerable are those who are in fairly good health, comparatively free from dyspnea and who fail to give a history

of recurrent attacks of rheumatic fever. Patients with aortic regurgitation alone or in combination with mitral valvular disease seem to develop the disease more often than those with distinct signs of mitral stenosis. It is exceedingly rare in syphilitic aortic insufficiency, in individuals without previous cardiac murmurs, and in patients with hypertension. It is practically unknown in patients with a history of previous attacks of heart failure or established auricular fibrillation and, to my knowledge, it has been reported as following a coronary occlusion in only one case.[12]

Of the congenital defects, the commonest predisposing lesion seems to be congenital bicuspid aortic valves, and a patent ductus arteriosus. In table 2 I have summarized the various conditions in which it has been observed.

TABLE II

Conditions in Which Bacterial Endocarditis Has Been Observed in Man

1. Rheumatic Heart Disease—acute or chronic
   - *a.* Aortic regurgitation
   - *b.* Aortic regurgitation with mitral insufficiency.
   - *c.* Mitral stenosis
   - *d.* Tricuspid insufficiency
2. Congenital Heart Disease
   - *a.* Bicuspid aortic valves
   - *b.* Patent ductus arteriosus
   - *c.* Coarctation of aorta
   - *d.* Subaortic stenosis
   - *e.* Patent interventricular septum
   - *f.* Pulmonary stenosis
3. Coronary Occlusion
4. Thrombotic Endocarditis (Chronic disease)

In short, it can be said that the patients who are likely to develop bacterial endocarditis are those with rheumatic or congenital valvular defects, in a good state of health, with a normal cardiac rhythm. It is not likely to develop in an individual with hypertension, or a normal heart, or in anyone with auricular fibrillation, or in a patient who has had previous attack of congestive heart failure.

In addition to the above factors there are other considerations in the pathogenesis of subacute bacterial endocarditis which require comment, namely, what are the factors predisposing damaged heart valves to infection by bacteria? what is the portal of entry? and why do the organisms localize?

The first question has been discussed and investigated by a number of observers. There have been two main views, namely, that the heart valves are infected by bacterial emboli focalizing in the valves, and that the organisms invade the valves from the outside. That is to say, it is an infection of the surface of the valve.

The chief argument against intravascular emboli being the sole cause of infection of the heart valves is the fact that it is not possible to demonstrate blood vessels in the heart valves of all individuals. On the other hand, it can be shown that bacterial infection of heart valves is most often superficial and the bacteria occur at the periphery of the thrombi on the valves.

Leary,[13] Mallory and I [14] have demonstrated bacteria in the very early lesions of bacterial infection of the heart valves and endocardium, and the organisms seem to invade the valves from the surface. How then do microörganisms gain a foothold on an injured valve? It is the opinion of Pappenheimer and Von Glahn [15] that most cases of subacute bacterial endocarditis are due to an infection of rheumatic vegetations by microörganisms, and Grant, Wood and Jones [16] have brought forth convincing evidence that platelet thrombi are exceedingly common on damaged or injured valves, and these thrombi serve as peculiarly favorable areas for the localization of bacteria. They found in studying non-bacterial thrombotic endocarditis that these thrombi occurred on valves which were thickened and on the ones in which infective endocarditis is likely to develop. Moreover, Grant has demonstrated platelet thrombi on heart valves which had been experimentally damaged, showing that injury to a heart valve is followed by the deposition of a platelet thrombus. It is now known that non-bacterial thrombotic endocarditis occurs in a variety of conditions [8] and, in studying this condition further, I have found that these thrombi may become infected and produce a bacterial endocarditis. Table 3 summarizes the conditions in which I have observed non-infected thrombotic endocarditis and the cases in which such thrombi have become infected by bacteria.

TABLE III

Summary of the Conditions in Which Non-Infected and Infected Thrombotic Endocarditis Are Observed

Non-infected		*Infected*	
Chronic heart disease	3	Chronic heart disease	2
Leukemia	1	Leukemia	2
Appendix abscess	1	Carcinoma	
Pulmonary tuberculosis	2	Cervix	1
		Lung	2
		Stomach	1
		Hypernephroma	1
		Cirrhosis of liver	1
		Stone in the common bile duct	1

It seems clear that either thrombotic or rheumatic endocarditis may serve as a suitable area for bacteria to localize and gain a foothold, and since these thrombi are relatively free from leukocytes, microörganisms are destroyed with difficulty and are able to survive. Since bacterial endocarditis occurs very often in conditions which favor the development of thrombi on the valve leaflets (damaged valves, acute rheumatic and chronic diseases) it is not far-fetched to believe that these thrombi are an important predisposing factor in the pathogenesis of bacterial endocarditis.

I should not like to leave the impression that it is always necessary to have a previously damaged valve in order for bacteria to gain a foothold on the heart valves and thrive. Indeed, it is well recognized that some microorganisms focalize on previously normal heart valves, and it is highly possible, as suggested by Wadsworth, that acute injury to the heart valves by bacteria serves as an excellent predisposing factor for the localization of

infection. It is well worth recalling, however, that the majority of cases of *Streptococcus viridans* endocarditis occur in patients with previously damaged valves, and this must be taken into account in any discussion of the pathogenesis of the disease.

The question now arises regarding the circumstances that permit bacteremia and the portal of entry for the infecting organism? It is well recognized that it is often impossible to tell when the original invasion of bacteria took place, since the disease begins in most instances in an insidious manner and is not preceded by any previous noticeable infection that would serve as a focus of entry. Upon reflection, this does not seem at all curious since it would be surprising if green producing streptococci did not invade the circulating blood frequently since they are present in the mouth from a period shortly after birth and persist until death. That they invade the circulating blood in a variety of diseases has been amply demonstrated by Lichtman and Gross,[17] Epstein and Kugel,[18] and Swift and Kinsella,[19] and one knows that they often invade the blood following tonsillectomy and the extraction of teeth. There are now on record a number of cases of subacute bacterial endocarditis in which the disease first asserted itself following the extraction of teeth or tonsillectomy, or respiratory infections, and one is also familiar with the cases that follow local areas of suppuration.[20]

In addition to the presence of thrombi on the heart valves and the bacteremia, it is necessary to account for the localization of bacteria. It is a general rule in bacterial infections that the localization of bacteria in tissues is consistent only in the cases in which there are antibodies present. It has been demonstrated by Kinsella,[21] Wright,[22] Miller and Branch,[23] Libman,[24] and Swift [25] that the blood from patients with active infections and bacteremia shows agglutinins for the homologous organism and is actively bactericidal. Spink and I [26] have demonstrated that the blood from bacteremic cases is not only capable of killing the organisms which are present in the circulating blood but is often capable of killing many thousands of microbes which are added to it. Furthermore, and this we consider of significance, the blood of some normal individuals is highly bactericidal for most strains of *Streptococcus viridans* which have been isolated from cases of proved bacterial endocarditis.

To sum up the information regarding the pathogenesis of subacute bacterial endocarditis in man it would appear that a damaged heart valve, the presence of platelet thrombi, transient bacteremia, and the presence of antibacterial antibodies which aid in the clearing of the blood stream and the localization of bacteria are all important in determining the development of bacterial endocarditis.

Experimental Bacterial Endocarditis

Bacterial endocarditis has been produced experimentally in animals (rabbits,[27] dogs,[28] horses,[29] and chickens [30]) by several methods and by different

investigators. These observations are of great importance in understanding some of the features of the infection in man.

The observations of Herrmann [28] in regard to endocarditis in dogs are significant. He found that the normal heart valves of dogs were relatively immune to infection by *Streptococcus viridans* when large doses of organisms were injected intravenously. When, however, the aortic valves were injured, a large number of puppies died from the results of a spontaneous streptococcus endocarditis. This was also noticeable in parturient bitches. In all, 20 per cent of his dogs with experimental aortic regurgitation developed spontaneous streptococcus endocarditis. Of further interest, however, it was found that dogs with damaged heart valves were found to be uniformly susceptible to bacterial implantations of streptococci when they were injected intravenously. Similar observations have been made in dogs by Kinsella.[28] In addition, he found that it was easier to produce endocarditis in dogs when they had been partially immunized. Of considerable interest in respect to the development of endocarditis on the damaged heart valves of dogs are the observations of Grant [16] that platelet thrombi form on the heart valves shortly after they have been ruptured, and it is possible that they serve as foci for the localization of bacteria.

The same kind of experiments have been carried out in rabbits with somewhat similar results, with the exception of the fact that repeated injections of organisms into rabbits with normal heart valves are followed by endocarditis in a certain number of cases. Wright [22] has shown that infection of the valves is more likely to occur in animals that have been treated with vaccines so that demonstrable antibodies are present in the circulating blood. It can be shown, however, that when the valves of a rabbit are damaged their resistance to infection is greatly lowered.

The observations of Wadsworth [29] on the occurrence of endocarditis in horses are of the highest significance to our understanding of the pathogenesis of bacterial endocarditis. He found that endocarditis developed very frequently in horses that had been immunized against pneumococci. The infection of the heart valves usually took place after the animal had a high antibody titer in the circulating blood and there was no convincing evidence that the infection took place early in the course of the injections. The blood cultures of these animals remained sterile and the organisms in the vegetations were few and could be cultured from the valves with difficulty, and were found in sections of the heart valves in only small numbers at post mortem.

In short, the findings in the horses studied by Wadsworth are similar in many respects to the "bacteria free" cases in man. That is to say, the endocarditis is active, the blood remains sterile. It is perhaps important to recall that endocarditis was produced in these animals without mechanical injury to the heart valves and it did not develop until there was a high antibody titer in the blood, a condition favoring the localization of bacteria.

To sum up this discussion, it may be said that infection of the heart valves is seen most often in animals following mechanical injury and the injection of microörganisms intravenously. Following mechanical injury to heart valves, platelet thrombi form and serve as a focus for the localization of bacteria; and while infection may occur spontaneously, it is most frequent following the injection of bacteria. Furthermore, when there is no previous injury to the valves, endocarditis develops more frequently following repeated injections of organisms into animals which develop active bactericidal antibodies. It would appear, then, that injury to the heart valves, the presence of antibodies, and bacteremia are all important and necessary in the pathogenesis of bacterial endocarditis. It is not at all unlikely in many instances, as suggested by Wadsworth, that the original injury to the valves is bacterial in origin since Leary and Mallory and I have demonstrated bacteria in very early lesions on the heart valves and endocardium.

Immunologic Studies in Bacterial Endocarditis

The immune reactions that can be demonstrated in the circulating blood of patients with bacterial endocarditis have been studied by Kinsella,[21] Wright,[22] Miller and Branch,[23] Swift,[25] Libman,[24] and ourselves. Inasmuch as these studies have a direct bearing on the problem of the pathogenesis of bacterial endocarditis they are presented in detail. While Kinsella was unable to show that there was any constant identity between the various strains of streptococci isolated from cases of bacterial endocarditis, he demonstrated quite conclusively that the patient's blood serum contained agglutinins and complement fixing antibodies for homologous strains of organisms. Miller and Branch demonstrated homologous agglutinins in their case and Wright [22] found that the blood of septicemic cases contained antibodies and was actively bactericidal. Moreover, in animals with bacterial endocarditis there was evidence of antibody production even in the face of an increasing septicemia. Wright considered the bacteremia in bacterial endocarditis to be a secondary phenomenon resulting from an escape of organisms from the lesions in the heart valves and thought that the bacteria increased in the blood stream of his animals because they multiplied in the lesion and were discharged faster than they could be removed. That this is true in man seems to be proved from the remarkable case of subacute *Streptococcus viridans* septicemia which was cured by excision of an arteriovenous aneurysm of the external iliac artery and vein, reported by Hamman and Rienhoff.[31] In this case, the removal of the focus (vegetations in the aneurysm) was followed by a clearing of the blood stream and complete recovery. This case seems to prove beyond any doubt that the bacteremia in these cases is an overflow phenomenon. In common with Wright, I have found that the cases which are negative are always negative, and since numerous blood cultures were taken during life in all of the cases

reported herewith, it is unreasonable to suppose that faulty technic was responsible for our failure to isolate the organisms during life.

Within recent years it has been found by Howells and Corrigan,[32] Levine,[33] Derrick and Fulton,[34] and Swift [25] that patients with subacute bacterial endocarditis fail to show skin reactions to filtrates of streptococci and we have confirmed these findings in 10 instances. This examination may be of significance in the diagnosis of obscure cases of bacterial endocarditis.

While it has not been proved in the human cases that the reason for the negative blood cultures during life is the presence of a high antibody titer

TABLE IV

Whole Blood Killing Power of Patients with Bacterial Endocarditis and Bacteremia
Maximum number of organisms killed by 0.5 c.c. whole blood. Homologous organisms.

	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-7}
Patient 1	0	0	0	0	0	0	0	5
Normal control	0	0	0	0	0	0	0	
Patient 2	0	0	0	0	0	0	0	2
Normal control	0	0	0	0	0	0	0	
Patient 3	0	0	0	0	0	0	0	2
Normal control	0	0	0	0	0	0	0	
Patient 4	0	0	0	0	0	0	0	29
Normal control	0	0	0	0	0	0	0	
Patient 4	0	0	0	0	0	0	0	29
Normal control	0	0	0	0	0	0	0	
Patient 5	+	+	0	0	0	0	0	5
Normal control	+	0	0	0	0	0	0	
Patient 6	+	+	+	0	0	0	0	6
Normal control	+	+	+	+	0	0	0	
Patient 7	+	+	+	0	0	0	0	11
Normal control	+	0	0	0	0	0	0	
Patient 8	+	0	0	0	0	0	0	12
Normal control	+	0	0	0	0	0	0	"
Patient 8	+	0	0	0	0	0	0	"
Normal control	+	0	0	0	0	0	0	"
Patient 8	+	+	0	0	0	0	0	"
Normal control	+	0	0	0	0	0	0	"
Patient 8	+	+	+	+	0	0	0	"
Normal control	0	0	0	0	0	0	0	"
Patient 8	+	+	+	+	0	0	0	"
Normal control	0	0	0	0	0	0	0	"
Patient 9	+	+	+	0	0	0	0	"
Normal control	+	+	+	+	0	0	0	"
Patient 10	+	+	+	+	0	0	0	"
Normal control	+	+	+	+	0	0	0	"

of the blood there is suggestive evidence, from studies on animals and in particular from the studies by Wadsworth, that such is the case. An additional factor is the small numbers of organisms present in the vegetations.

Baehr suggests that some patients with bacterial endocarditis develop an immunity to the infecting organism which is of sufficient degree to kill off the bacteria shortly after the onset of the disease. In this way, he explains the bacteria-free cases. From numerous observations on man and animals it does not seem unreasonable to suppose that the reason for the negative blood cultures is due to the fact that the organisms are removed from the circulating blood as rapidly as they enter it. That they are present in the blood from time to time is attested by the presence of embolic phenomena in these cases. The reason they continue to live in the vegetations of the heart valves is probably due to the fact that the bacteria are situated in an area where there are relatively few leukocytes or tissue phagocytes and the bactericidal action can not operate effectively.

Studies on the bactericidal power of the whole blood of patients with bacterial endocarditis and bacteremia indicate that normal individuals are often able to kill large numbers of organisms that can be isolated from the blood of patients with endocarditis. Likewise, the patients with bacterial endocarditis can do the same. This is illustrated in table 4 and chart 1.

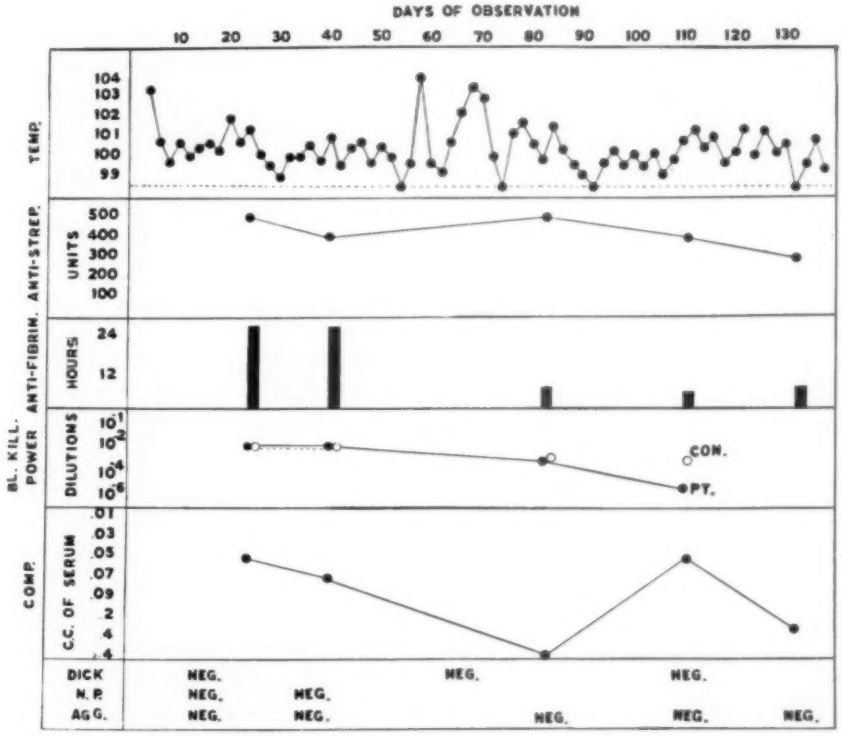

CHART 1. The temperature chart together with the various immune reactions that were followed in a patient with bacterial endocarditis.

In short, then, it would appear that normal individuals as well as patients with bacterial endocarditis possess antibacterial antibodies against some strains of *Streptococcus viridans* derived from endocarditis. This is suggestive evidence of a defense mechanism for the clearing of the blood stream of bacteria, once they gain entrance to the circulation. While it is not known whether all of the patients who have immune bodies in their circulating blood at the time of an active infection have had antibodies before the onset of infection, it is suggested by our observations on some normal individuals, that this is possible; although Swift [25] records a case in which agglutinins against the homologous organism were not present before infection and appeared after its development. This is a question requiring further study.

Summary and Conclusions

A group of 15 cases of active bacterial endocarditis without bacteremia is described and summarized. For purposes of discussion they were divided into five groups: (1) those with right-sided valvular disease, multiple pulmonary infarcts, and jaundice; (2) patients with renal insufficiency; (3) patients with heart failure; (4) patients with splenomegaly and anemia; and (5) patients with hemiplegia.

All of the patients had physical signs of valvular disease. Non-syphilitic aortic regurgitation was present in ten. The mitral valve was involved alone in two and the tricuspid alone in three.

There was no essential difference in the clinical course of the patients with bacteremia and in those without bacteremia with the possible exception of the fact that the non-bacteremic cases were more apt to have renal insufficiency as an outstanding feature of their illness.

The pathogenesis of bacterial endocarditis as it is observed in man and the experimental animal was reviewed and it was pointed out that the following factors are significant: a previously damaged valve, the presence of platelet thrombi on the valves, a transient bacteremia and the presence of antibodies that encourage the localization of bacteria.

Bactericidal studies in the blood of patients with bacterial endocarditis were presented, and it was concluded that some normal individuals as well as patients with bacterial endocarditis have antibodies which are capable of killing organisms derived from cases of bacterial endocarditis.

From the foregoing discussion it seems reasonably plain that bacterial endocarditis can be produced in animals under the same circumstances as exist in man; namely, the presence of damaged valves, platelet thrombi on the valves, bacteremia, and the presence of antibodies. There also is highly suggestive evidence that the human cases with negative blood cultures have a condition analogous to the experimental endocarditis of horses as described by Wadsworth. This, however, requires further study and proof. In any event, it is well to recognize this group of cases since they aid in understanding the infection and should encourage one to look for ways of destroying organisms in the valves.

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DISTURBANCES OF RATE AND RHYTHM IN ACUTE CORONARY ARTERY THROMBOSIS *

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INTRODUCTION

INVESTIGATORS [1-5] during the nineteenth century observed that ligation of the coronary arteries in animals very frequently produced cardiac arrhythmias either transient or severe enough to cause cardiac standstill, but their exact nature was not defined until the beginning of the present century. In 1909, Lewis [6] reported that after ligation of the left coronary artery multiple premature beats were recorded by venous pulse and electrocardiographic tracings. These frequently formed paroxysms of ventricular tachycardia from which ventricular fibrillation sometimes developed. Subsequent workers [7-12] confirmed these observations. Recently, in addition, de Waart et al.,[11] after tying off the right coronary artery found sinoauricular and auriculoventricular block. In all these observations it is noteworthy that auricular fibrillation and flutter were rarely encountered, and auricular and nodal tachycardia only occasionally.[9]

In man also, the majority of authors [13-21] have noted the presence of arrhythmias in coronary artery thrombosis. While White [20] thinks they occur in only a small number of cases, Levine [22] observed them in more than one-fourth of his series. The incidence of the significant arrhythmias, that is, those other than premature beats, in several large series [22-31] varies between 9 and 27 per cent, the average in over 800 cases being 17 per cent. As in animals, the most common irregularity is premature beats, usually ventricular, which occurred in about one-quarter of the cases. Next in order of frequency is auricular fibrillation. In the reports mentioned above its incidence was usually 6 to 7 per cent, although Levine's [22] figures were as high as 23 per cent and Meakins and Eakin's [26] 14.5 per cent. Brill,[32] too, observed that it frequently appeared early in coronary thrombosis.

The other arrhythmias, auricular flutter, auricular and nodal tachycardia, ventricular tachycardia, nodal rhythm and heart block, in the experience of all authors [23-31] occurred in only a small percentage of cases. Auricular flutter was observed by Parkinson and Bedford [24] and Jervell [29] in 3 to 4 per cent of cases and by Howard [27] in only 0.6 per cent. However, of nine fatal cases of coronary artery thrombosis described by Longcope,[33] four had auricular flutter. Other authors [28, 34, 35] also observed this ar-

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rhythmia in coronary artery thrombosis. Similarly, auricular and nodal tachycardia occurred infrequently.[24, 28, 36, 37] Sinoauricular block,[29, 38] sinus bradycardia [39, 40] and nodal rhythm [38, 40, 41, 42] have been encountered but once or twice in any one series. The average incidence of heart block, partial and complete, is 2 to 5 per cent,[22-31] although Appelbaum and Nicolson [37] found three instances in 30 cases. Salcedo-Salgar and White,[43] in a recent study of heart block in more than 300 cases of coronary thrombosis, found the incidence to be 4.2 per cent; this figure included 10 cases of partial and only four of complete block. In marked contrast is the experience of Schwartz [44] who over a period of a few years observed 15 cases of complete heart block with Stokes-Adams syndrome precipitated by coronary thrombosis. In this connection may be mentioned the recent analysis by Graybiel and White [45] of 72 cases of complete heart block of which approximately 10 per cent followed an acute coronary thrombosis.

Because of the frequency of ventricular tachycardia in experimental coronary ligation [6-12] its importance in coronary artery thrombosis has been emphasized in numerous case reports in the literature.[8, 22, 42, 46-59] It is significant, however, that most of the authors have reported one or only a few cases of coronary artery thrombosis with ventricular tachycardia, or rarely, a small series of ventricular tachycardia in which the chief etiological factor was recent or old myocardial infarction.[60-63] Analysis of large series of cases of coronary artery thrombosis, however, gives a truer perspective of the rarity of this arrhythmia. Although Levine [63] intimates that it occurs in approximately 5 per cent of cases, in 470 cases in the series mentioned above,[23-31] there were but three cases, an incidence of 0.6 per cent.

It has been found that not infrequently two or more arrhythmias occur simultaneously or in close association.[35, 38, 41, 42, 53, 57, 64, 65] Hamman [13] considered such a sequence diagnostic of coronary artery thrombosis.

Material

An analysis of the arrhythmias found in 300 cases of coronary artery thrombosis is presented in this report (table 1). Excluding premature beats, present in one-quarter of the cases, the incidence of arrhythmias was 14 per cent. Forty-two patients presented the following 46 irregularities:

Auricular fibrillation	22	
Auricular flutter	3	
Paroxysmal tachycardia	9	
auricular		3
nodal		2
ventricular		1
undetermined		3
Nodal rhythm	3	
Wandering pacemaker	1	
Heart block	8	
incomplete heart block with dropped beats		3
complete A–V dissociation		3
combination of both types		2

Prolongation of the P–R interval, which was very common, and bundle-branch block are not included in this paper as they will form the material of a future article. For the same reason A–V heart block will not be considered in great detail.

Significant differences were observed between patients with arrhythmias and those with regular rhythm (table 1). In the former group, the ratio of men to women was 2.3 : 1, in the latter 4 : 1; apparently women are more prone to develop irregularities than men. This applied particularly to auricular fibrillation and heart block. The average age was slightly higher in those with arrhythmias. Furthermore, hypertension and cardiac enlargement occurred in four-fifths of the cases with an arrhythmia, whereas in those without, hypertension was present in 65 per cent and cardiac enlargement in only 60 per cent. Heart failure also was more common when an arrhythmia existed, that is, in 85 per cent as compared to 70 per cent. It is obvious, then, that arrhythmias occurred in the more severely ill patients, a fact further supported by the high mortality rate in this group, 39 per cent as against only 22 per cent in the remainder of the series. The mortality rate for the entire series of 300 cases was 26 per cent. Most of the deaths were in the group with auricular fibrillation and complete heart block. That the arrhythmia may have been merely one expression of the severity of the attack and not the cause of death, however, is probable in view of the fact that half the patients died some time after the cessation of the arrhythmia.

Almost half the arrhythmias appeared during the first three days succeeding the attack and the majority during the first week. In some cases it followed immediately the onset of the attack. However, the arrhythmia may set in at any time, even in the third week. The duration of the arrhythmia was usually short. In over half the cases it lasted 24 hours or less, and in some only a few hours. Auricular fibrillation and paroxysmal tachycardias were as a rule, transitory; heart block and nodal rhythm usually persisted longer, occasionally several weeks.

It is interesting that the presence of previous occlusions did not increase the incidence of arrhythmias. This would indicate that the latter depend upon the acute changes in the heart.

Premature Beats

Premature beats occurring in 77 patients or one-quarter of the series was by far the most common irregularity encountered. They were ventricular in type in 46 cases, auricular and ventricular in 15, auricular alone in 14 and nodal in two. Multiple premature beats were found very frequently and in nine patients there was bigeminal or trigeminal rhythm (figures 7 and 9). The mortality rate in this group did not differ from the average for the entire series although it should be noted that when auricular or both auricular and ventricular premature beats occurred, the mortality rate was higher (35 to 40 per cent). But this finding might not hold true

TABLE I

Analysis of the Arrhythmias in 300 Cases of Coronary Artery Thrombosis

	Total Control Series	Arrhythmias Excluding Premature Beats	Premature Beats	Auricular Fibrillation	Auricular Flutter	Nodal Rhythm	Paroxysmal Tachycardia	Complete Heart Block	Partial Heart Block
No. of cases	300	46	77	22	3	4	9	5	3
Incidence		14.5%	25.7%	7.3%	1.0%	13.0%	3.0%	1.7%	1.0%
Average age	56	58	56	60	61	53	54	61	57
Ratio—male: female	3.9 : 1	2.3 : 1	6 : 1	2.1 : 1	3 : 0	4 : 0	8 : 1	1 : 4	1 : 2
Previous attack	47.7%	47.8%	59.7%	50.0%	100%	0	33.3%	80.0%	33.3%
Previous hypertension	64.6%	80.4%	75.3%	86.3%	66.6%	50.0%	88.8%	100%	33.3%
Enlarged heart	60.3%	78.2%	72.7%	81.8%	100%	25.0%	88.8%	80.0%	66.6%
Heart failure	71.0%	84.8%	74.0%	81.8%	100%	25.0%	100%	100%	100%
Mortality	25.7%	38.0%	28.5%	45.4%	66.6%	0	22.2%	80.0%	0
During arrhythmia		19.0%		22.7%	33.3%		0	60.0%	
Later in attack		19.0%		22.7%	33.3%		22.2%	20.0%	
Onset—1–3 days		20	20	7		3	3	5	2
4–7 days		11	16	8	1	1	1		1
2nd week		11	14	5	2		4		
3rd week		4	17	2			1	3 (death)	
Duration—1 day or less		25	4	12	2		8		1
2–3 days		5	30*	3		1			1
1–2 weeks		11	15	5	1	3		1	
2–3 weeks		1	5				1		
1–2 months		2	6	1				1	
Permanent		2		1					1
Average vent. rate				120–150	85–150	60–70	120–180	20–75	50–100

* Two to seven days' duration.

in a larger series. Also the fact that the incidence of heart failure was practically the same as in the whole series is evidence that the clinical significance of premature beats is not important.

It has often been stated [12, 66, 103] that the appearance of frequent ventricular premature beats may be the forerunner of ventricular tachycardia. Yet, this occurred only once in our series, when a fleeting paroxysm of ventricular tachycardia was observed during the course of a bigeminal rhythm (figure 9).

Auricular Fibrillation

Auricular fibrillation was found 22 times and occurred more frequently in women than in men. The average age of these patients was somewhat higher than in the general series. The incidence of increased arterial tension, enlarged heart and heart failure was definitely greater than in the control group and the mortality rate was high, 45 per cent. The latter was in large degree dependent on the heart failure since half the deaths occurred after the arrhythmia had spontaneously remitted. The average ventricular rate was 120–150 beats per minute (figures 1 and 2) which was undoubtedly associated with the high incidence of heart failure. Several cases, however, had a slow ventricular rate even without the use of digitalis.

The onset of auricular fibrillation usually occurred during the first few days and in two-thirds of the cases during the first week. It is significant that in 12, or more than half of the patients, its duration was 24 hours or less. In one instance it lasted two months and then ceased spontaneously, and in another it became permanent after digitalization. In five patients the irregularity was intermittent, alternating with periods of sinus rhythm.

With a view to the possibility that this arrhythmia might be ascribed to a lesion in a specific area of the heart, electrocardiograms were grouped into types associated with infarction of the anterior (Q_1T_1) or posterior (Q_3T_3) surface of the left ventricle. It was found that with auricular fibrillation, the infarction was as frequent on the anterior as on the posterior surface of the heart. In five of these cases examined at necropsy the right and left coronary arteries were equally occluded.

Digitalis was administered to two patients after the onset of the auricular fibrillation because of severe heart failure. One of these died suddenly on the eighteenth day (figure 3) and the other developed permanent fibrillation although the heart failure was controlled. Two other patients received digitalis before the onset of the fibrillation but it is not possible to state whether the appearance of the arrhythmia was related to the drug.

Auricular Flutter

There were three patients with auricular flutter, two of whom died (figures 3 and 4). Heart failure and enlarged hearts were found in each instance and all had had one or more previous attacks of coronary throm-

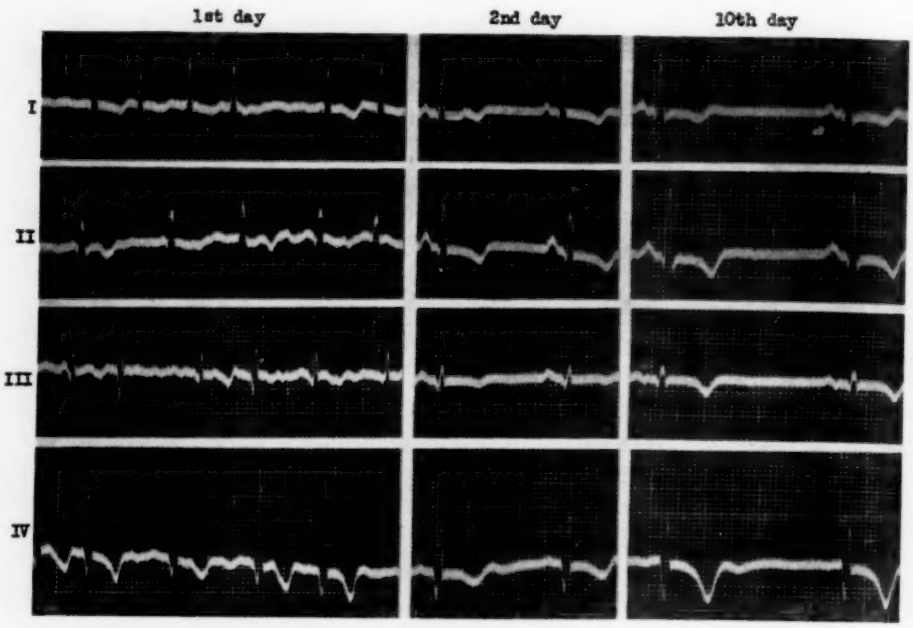

FIG. 1. D. S., male, aged 61. Acute and old coronary artery thrombosis. Recovery. Paroxysmal auricular fibrillation and sinus bradycardia.

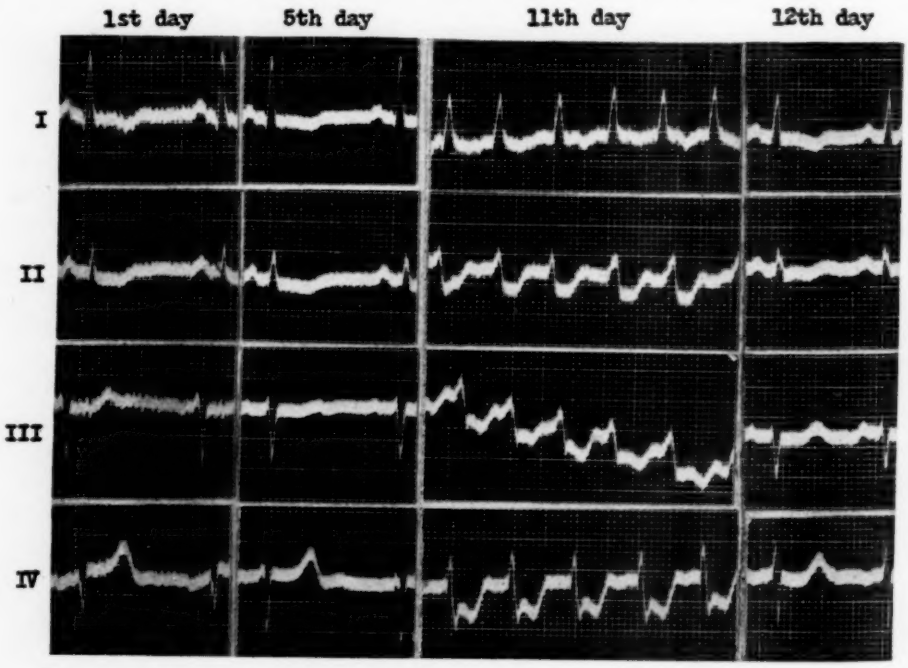

FIG. 2. Auricular fibrillation. Acute coronary thrombosis in 56 year old male. (J. K.) Died twenty-fourth day. P. M. Thrombosis of LAD, left and right circumflex coronary arteries.

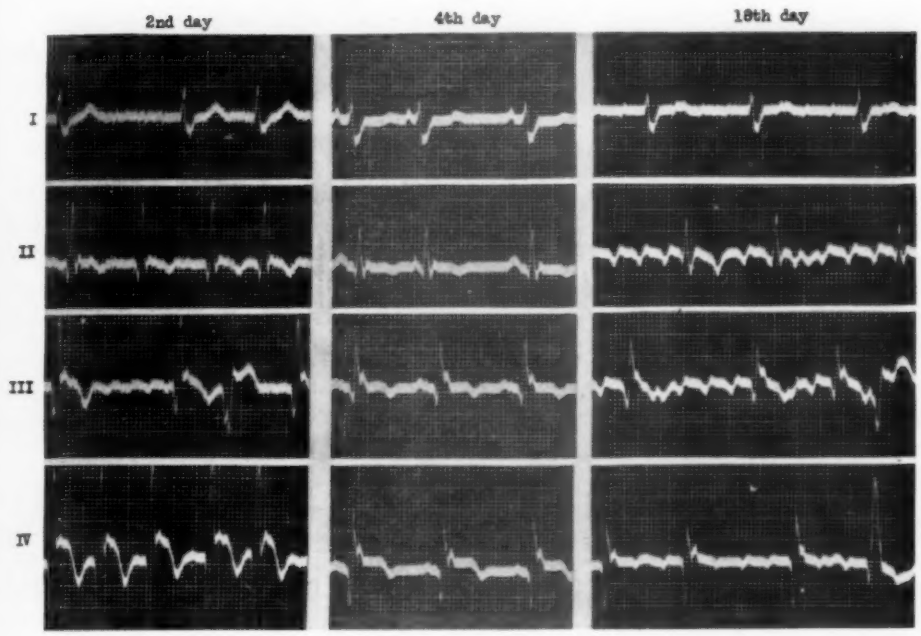

FIG. 3. S. L., male, aged 67. Old and acute coronary artery thrombosis. Paroxysmal auricular fibrillation and flutter. Sudden death on the eighteenth day. P. M. Acute right, old LAD and right coronary thrombosis. Posterior infarction.

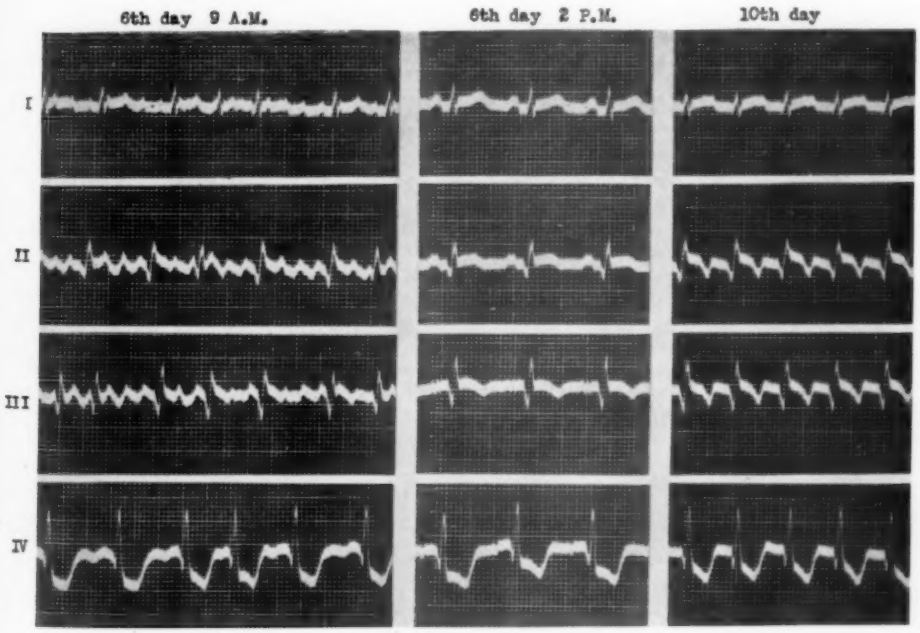

FIG. 4. S. C., male, aged 58. Old and acute coronary artery thrombosis. Paroxysmal auricular flutter. Sudden death on thirteenth day.

bosis. In one of the fatal cases the auricular flutter was a transient episode during auricular fibrillation (figure 3). The two fatal cases had both received digitalis, one during the arrhythmia and one before it set in.

Nodal Rhythm

There were three cases with nodal rhythm and one with wandering pacemaker (figures 5*A* and 6). All four patients survived, probably because the ventricular rate was normal, between 60 and 70 beats per minute. The arrhythmias disappeared without treatment within a week. Not all cases of nodal rhythm and shifting pacemaker are due to right coronary artery occlusion as one might expect, for two patients had electrocardiographic signs of anterior wall infarction. Thus the S–A node may be compromised by occlusion of the left coronary artery, either by involvement of its nutrient blood vessel or nerve supply.

Paroxysmal Tachycardia

Paroxysmal tachycardia occurred in nine patients. The average ventricular rate was 150 beats per minute. Although all nine patients had heart failure and eight an enlarged heart and hypertension, the duration of the arrhythmia was 24 hours or less in eight of the nine, and only two died. Of the nine cases, three were auricular (figures 5*B* and 7), two nodal (figure 8) and one ventricular (figure 9). Although the focus of origin was undetermined in three because electrocardiograms were not obtained during the arrhythmia, the clinical appearance was that of an auricular tachycardia.

A word should be added concerning ventricular tachycardia. With constant supervision and frequent electrocardiograms it was observed only once in the 300 cases examined.* Its duration was extremely brief, a few hours, and it remitted without treatment. This observation emphasizes the rarity of ventricular tachycardia in man.

Only two patients with paroxysmal tachycardia received treatment. One with auricular tachycardia who recovered received one dose of 6 grs. of quinidine sulphate. The arrhythmia ended 10 hours later but probably was not influenced by the drug. Another patient with nodal tachycardia was given 54 grs. of quinidine but died of a cerebral embolus four days after cessation of the tachycardia.

Heart Block

Although increased P–R intervals occurred very often, incomplete heart block with dropped beats or complete A–V dissociation was found but eight times in the 300 cases. Three patients had complete heart block alone with

* Since these data were collected, two other cases of ventricular tachycardia have been observed. In one, a 42 year old woman, the arrhythmia persisted despite quinidine therapy by mouth and intravenously and the patient died after two days. Septal infarction without recent thrombosis was found at post mortem. In the second case, a male aged 38, the tachycardia lasted about one day and ceased spontaeously. The patient recovered.

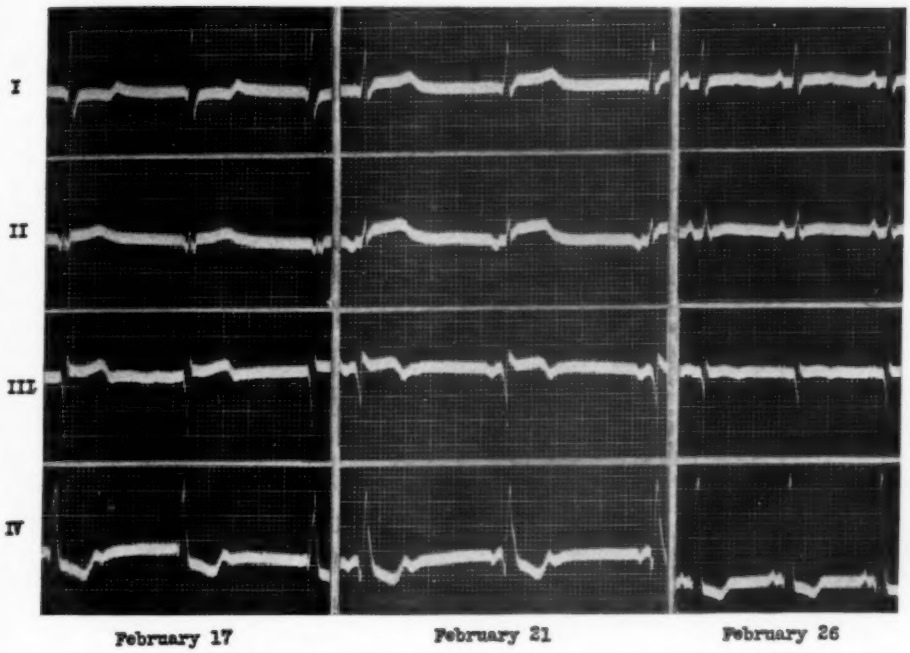

FIG. 5*A*. S. H., aged 62. Acute coronary occlusion. Nodal bradycardia.

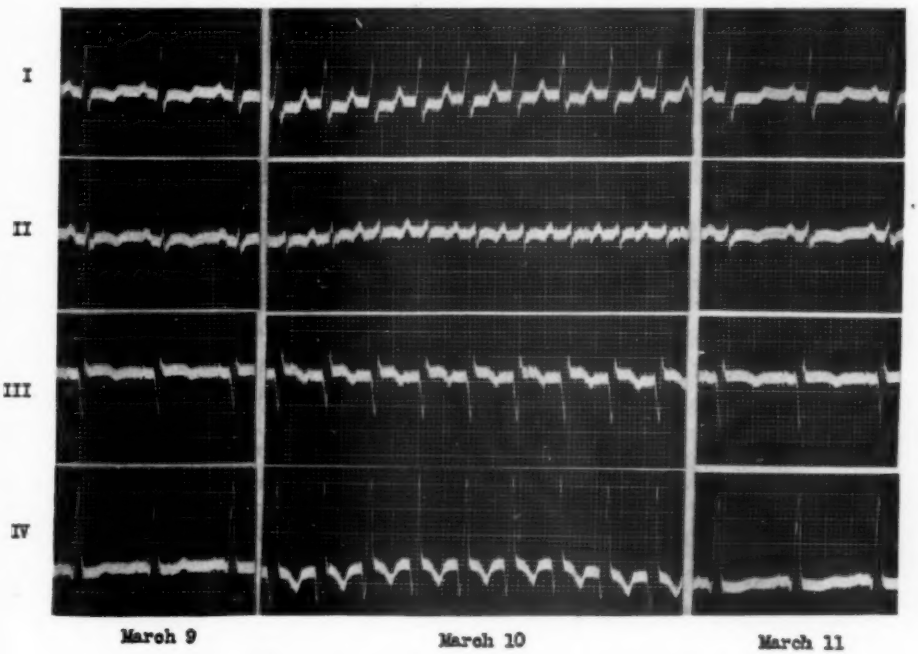

FIG. 5*B*. Same patient. Paroxysmal auricular fibrillation.

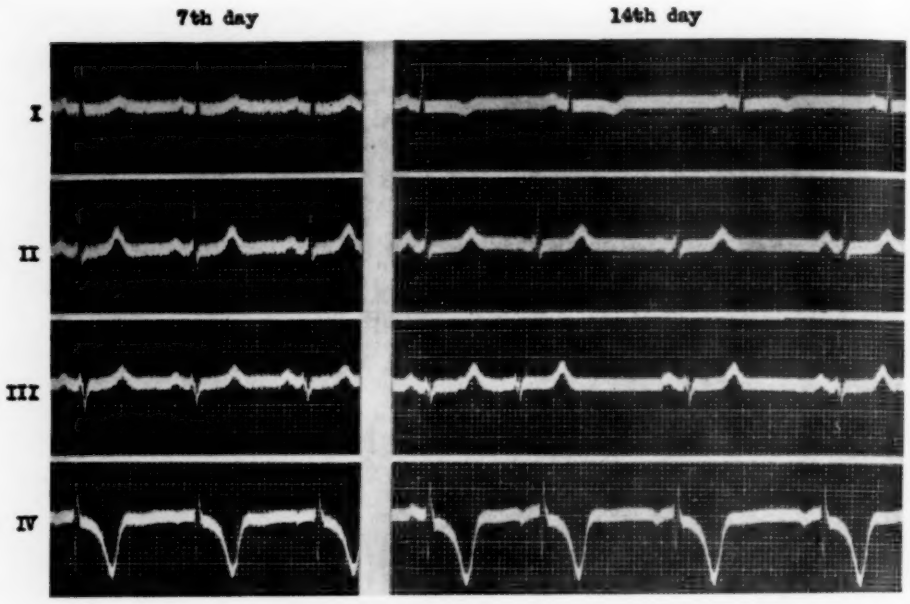

FIG. 6. C. Z., male, aged 48. Coronary thrombosis. Shifting pacemaker. Duration one week.

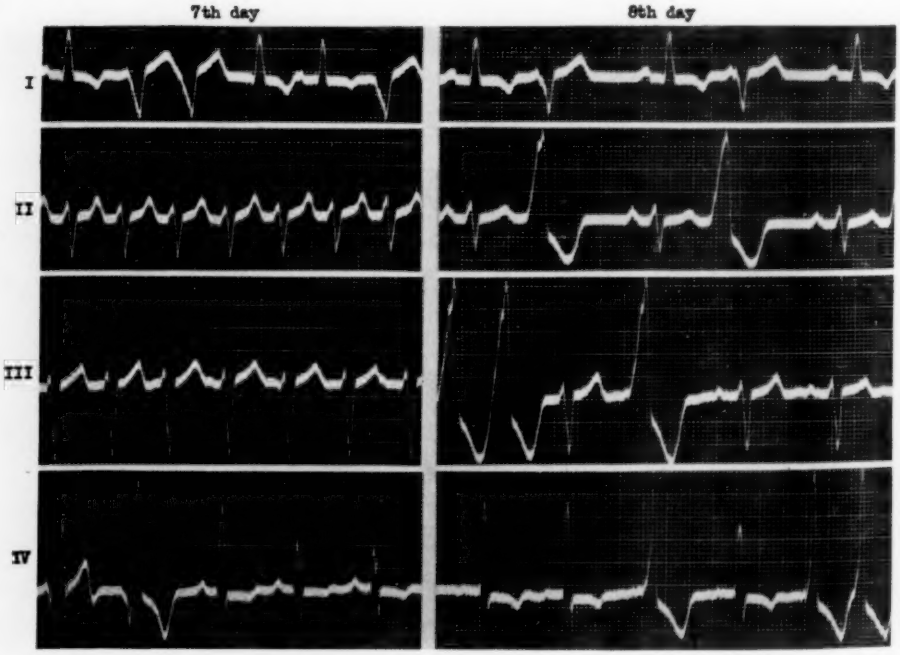

FIG. 7. C. L., male, aged 48. Coronary thrombosis. Auricular tachycardia, ventricular bigemini. Recovered.

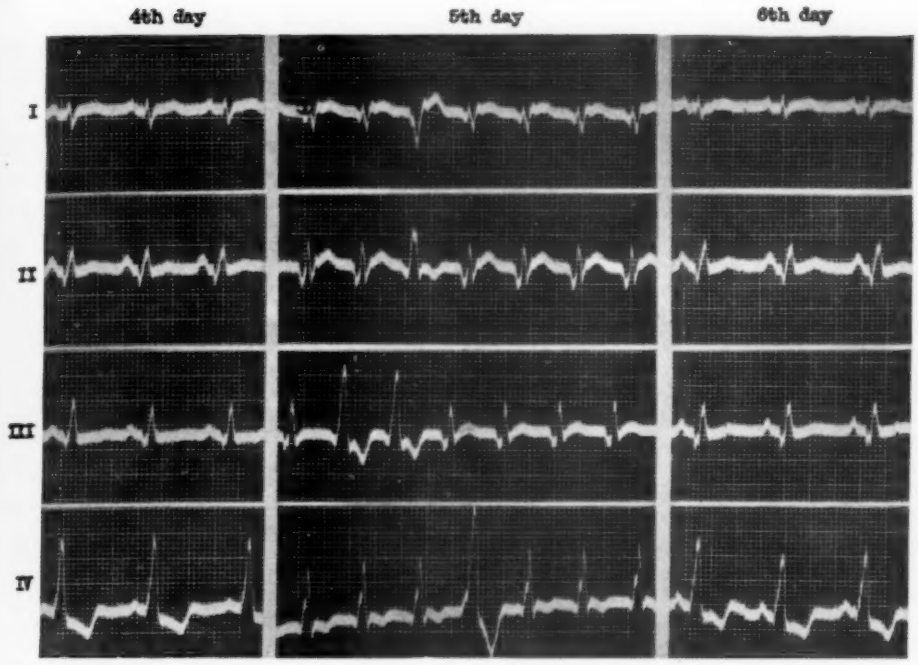

FIG. 8. L. D., male, aged 61. Coronary thrombosis. Nodal tachycardia. Recovery.

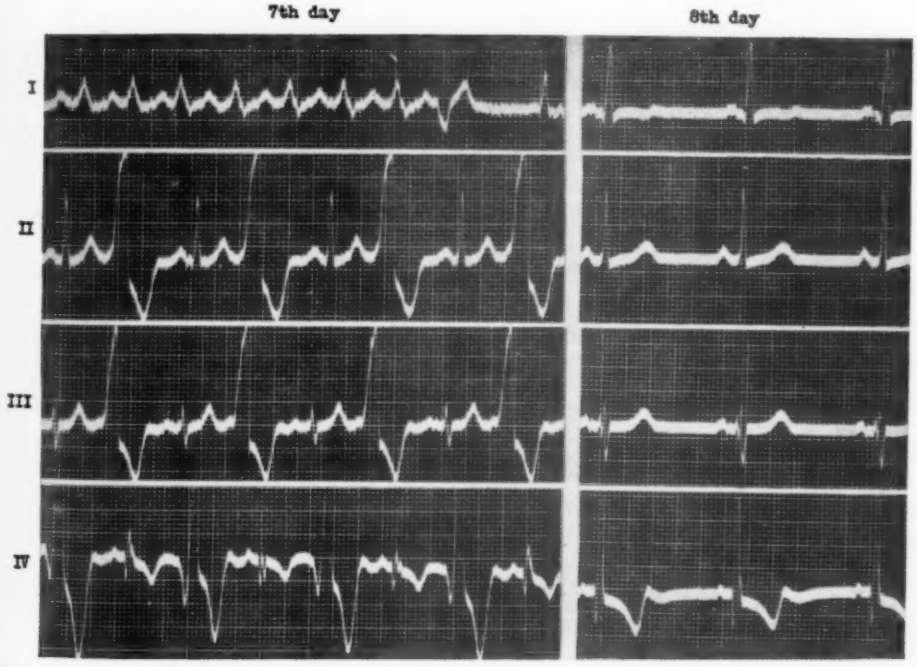

FIG. 9. E. M., male, aged 56. Coronary thrombosis. Ventricular tachycardia and bigemini. Recovered.

ventricular rates between 20 and 40 beats per minute (figure 10). They all had hypertension, an enlarged heart and heart failure. These patients all died within three days after the onset of the arrhythmia. In two other patients the arrhythmia varied between incomplete and complete heart block; one of these died of heart failure soon after the rhythm had returned to normal. Finally, there were three patients who had incomplete heart block alone. The ventricular rate in these cases was higher, 50 to 100 beats per minute, and all three survived. In one, the incomplete heart block was still

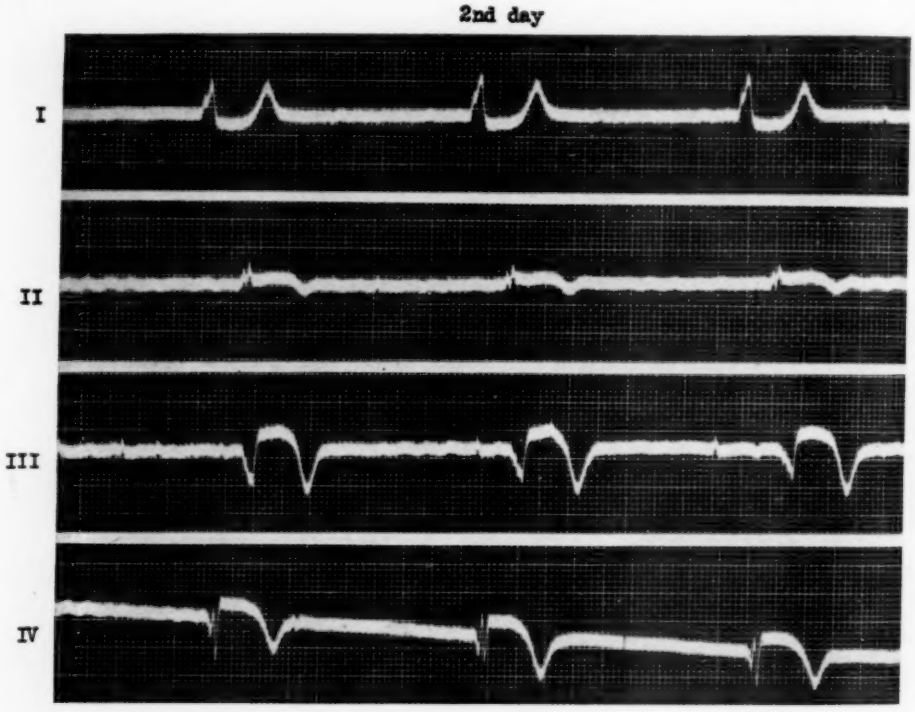

FIG. 10. C. B., female, aged 72. Coronary thrombosis. Complete heart block and auricular fibrillation. Death on fourth day. P. M. Right coronary thrombosis. Infarction posterior left ventricle and septum.

present one year after the attack. In the other two, normal sinus rhythm returned gradually within one week.

Four of the five patients with complete heart block came to postmortem examination and in each instance there was occlusion of the right coronary artery with infarction of the posterior wall and septum, with or without occlusion of the other arteries, findings which confirmed those of previous investigators [22, 38, 44, 67, 68] who had noted the association between complete heart block and this specific pathological lesion.

One patient with complete heart block received adrenalin before admission to the hospital but with no effect. One patient who showed both com-

plete and incomplete heart block at different times received atropine and ephedrine sulphate, again with no effect. The three patients who had incomplete heart block received no treatment and survived.

The heart rate in this group of cases deserves emphasis. The three patients with complete heart block who died were semi-comatose with rates between 20 and 40 beats per minute when admitted to the hospital. We believe that in these cases the outcome depended on the ventricular rate; when it is below 40, the prognosis is poor.

Association of Arrhythmias

In three cases two or more significant arrhythmias (figures 3 and 5) were associated and in 10 cases a significant arrhythmia was associated with multiple premature beats as, for example, a ventricular bigemini interrupted by paroxysms of auricular tachycardia (figures 7 and 9). One patient developed nodal rhythm during the first week of his illness, auricular fibrillation during the second week and auricular tachycardia during the third week (figures 5*A* and 5*B*).

Normal Heart Rate

In 134 patients (44.6 per cent) the heart rate throughout their illness was between 61 and 100 beats per minute (table 2). Enlarged hearts and heart failure were found in only one-half of these, an incidence less than the average of our series. The majority of patients were in their first attack of thrombosis. The mortality rate was only 6 per cent. Therefore, a patient whose heart rate does not go above 100 beats per minute has a very good outlook.

Table II

Heart Rate in 300 Cases of Coronary Thrombosis

	Normal Heart Rate	Sinus Tachycardia	Sinus Bradycardia
No. of cases	134	158	70
Incidence	44.6%	52.6%	23.3%
Average age	[illegible]	57	54
Ratio—male: female	4 : 1	3.6 : 1	10.7 : 1
Previous attack	44.0%	50.0%	38.6%
Previous hypertension	61.9%	65.8%	60.0%
Enlarged heart	48.5%	69.6%	42.8%
Heart failure	53.9%	84.2%	47.1%
Mortality	6.0%	39.9%	2.8%
Average ventricular rate	61–99	100–150	46–60

Sinus Tachycardia

We have emphasized in a previous study [69] the importance of tachycardia both as a prognostic sign in coronary thrombosis and as an index of the

degree of heart failure. When the cardiac rate rose above 100, the incidence of cardiac enlargement and heart failure as well as the mortality rate rose, 40 per cent of these cases ending fatally (table 2). The significance of heart rate is particularly evident in those with a rate of 120 or more; heart failure was almost universal and the mortality rate 54 per cent as against 29 per cent in the group with a rate 100 and 120. As previously stated, in patients with a rate between 60 and 100, the mortality rate was only 6 per cent.

Simple Bradycardia

A study of the clinical course of those patients whose heart rate at any time during the attack of coronary thrombosis fell to 60 or below, excluding cases of heart block, is of interest (table 2). These patients did extraordinarily well, and heart failure and mortality rate were minimal. In fact, none of the eight patients whose rate was between 40 and 50 and only two of the 62 whose rate was between 50 and 60 died. The average age of these patients was slightly lower than the average for the series; the majority had sustained their first attack and the incidence of enlarged hearts and heart failure was low.

Symptoms

The onset of an arrhythmia in patients with coronary thrombosis may be of considerable diagnostic significance. Occasionally, it is the first, perhaps the only, sign of the presence of thrombosis, corroborated by electrocardiogram. Therefore, even in the absence of pain, the sudden appearance of an arrhythmia may warrant a tentative diagnosis of coronary artery thrombosis.[13, 22, 25] The arrhythmia may occasion no symptoms other than palpitation. However, when the ventricular rate is very rapid, the coronary circulation of a heart already severely damaged may become so embarrassed as to cause precordial pain and shock which simulate another acute coronary artery thrombosis.[70–78] In our series, two patients who were recovering from the effects of an occlusion suddenly suffered a recurrence of severe precordial pain and shock. Electrocardiograms during this episode showed in one case (figure 2) auricular fibrillation with a ventricular rate of 150–200 and in the other (figure 5*B*), auricular tachycardia with a ventricular rate of 170; in addition there were definite R–T deviations characteristic of acute infarction. However, the diagnosis of another acute thrombosis had to be given up when within 24 hours the condition of the patient and the electrocardiogram spontaneously resumed their former status after regular sinus rhythm and a slow rate had returned.

The effect of a very slow ventricular rate, as in complete heart block, may also manifest itself clinically by syncope, convulsions and coma, that is, the Stokes-Adams syndrome. In our experience and that of most authors, the latter is rare in coronary artery thrombosis. However, Schwartz[44]

recently described 15 such cases, although it is possible that not all had coronary thrombosis as the diagnosis could be confirmed by electrocardiogram or necropsy in only a few cases. One of our patients with heart block entered and died in coma, and two others in semi-coma; in the former, an associated cerebral vascular lesion could not be ruled out. Another point not to be overlooked, as Levine [22] has emphasized, is that syncope in coronary thrombosis may result from insufficient cerebral circulation as a result of severe collapse. Such an occurrence was observed in one patient of our series.

Levine [22] was the first to point out the rarity of coronary artery thrombosis in patients with auricular fibrillation; he observed only one such case and in this the diagnosis was uncertain. Parkinson and Campbell [74] in 200 cases of paroxysmal auricular fibrillation found 12 associated with coronary thrombosis but in only two was the arrhythmia present before the acute attack. Brown [75] studied the incidence of coronary thrombosis in patients with auricular fibrillation and coronary sclerosis and found only two instances in 119 cases. In a similar study of 158 hypertensive patients with fibrillation Flaxman [76] found only three instances of coronary artery thrombosis. In our own series auricular fibrillation may have been present preceding the attack in two patients. The explanation for this antagonism between auricular fibrillation and coronary thrombosis is not clear to us.

The Mechanism of Production of Arrhythmias in Coronary Artery Thrombosis

When one considers the multiplicity of effects of coronary artery closure on the heart, it is not surprising that arrhythmias are often a complication. In the present state of our knowledge it is, of course, not possible to explain each arrhythmia with certainty. However, certain factors, such as *anoxemia, impaired nutrition* or *altered metabolism* of the heart muscle, increased *irritability, nervous reflexes, anatomical lesions* and *heart failure* are important in initiating any arrhythmia and all these are present to a striking degree in coronary artery thrombosis.

It is impossible to separate anoxemia and impaired nutrition or metabolism of the heart muscle. The effect of coronary thrombosis is not confined to the local area of infarction but disturbs the function of the heart as a whole. During the acute stage of shock there is a marked diminution of cardiac output and mean blood pressure and not only is there a local block in the coronary circulation at the site of the thrombosis, but the blood flow to the rest of the myocardium is reduced. The nutrition of the heart suffers, its metabolic activities are interfered with, and as Neuhof [64] early pointed out, such disturbances in the auricular musculature produce differences in refractory periods and delays in conduction which may throw the auricles into fibrillation. Carter and his coworkers [77] emphasized the relation between anoxemia and cardiac irregularities, particularly in coronary throm-

bosis. Anoxemia leads to the local accumulation of lactic acid which interferes with the development of the excitatory process and its normal propagation. Thus there may be a local area in which diminished conductivity or spontaneous excitation gives rise to an ectopic rhythm. In particular, anoxemia may decrease the refractory period in the auricles leading to the circus movement of auricular fibrillation and flutter. Carter refers also to the earlier observations of Greene and Gilbert [78] who, following rebreathing experiments in men and in animals, noted great slowing of rate, shifting pacemaker, nodal rhythm and progressive delay in A–V conduction. They emphasized the sensitivity of the S–A and A–V nodes to anoxemia but believed that the effect of anoxemia might be an indirect one through the vagus nerves. Resnik,[79] too, found that the S–A and A–V nodes and auricles were especially sensitive to anoxemia with the consequent slowing of the heart and shortening of the refractory period which predispose to auricular fibrillation.

Another mechanism for production of cardiac irregularity is the *irritability* of the local area of infarction, from which abnormal impulses or reflexes may arise. The area of infarction is a region of diminished blood supply, dying muscle and surrounding inflammatory reaction. As Condorelli [80] and Froment [62] have emphasized, it is a question whether the dying muscle or the surrounding inflammatory tissue acts as the irritable focus for the initiation of ectopic beats. Not only may the area of infarction initiate abnormal impulses but it may also interfere with the orderly conduction of the excitation wave through the ventricles. Further, abnormal *reflexes* may arise from this irritable focus either directly or as a result of anoxemia. The importance of the *vagus nerve* in these reflexes was demonstrated by Greene and Gilbert [78] who were able to abolish the arrhythmias due to anoxemia in dogs by cutting the vagus nerve. Some authors,[55, 62, 81, 82] finding ventricular tachycardia commonly associated with septal infarction, have suggested that damage to the septum and conduction system as well as local irritability are necessary for the production of ectopic rhythms of this type.

The importance of the various factors discussed above is appreciated when it is realized that, except in complete heart block, there is no correlation between the exact site of thrombosis or infarction and the type of arrhythmia. Since the right coronary artery supplies the A–V node and the bundle of His in 90 per cent of cases and the auricles and S–A node in 60 per cent of cases (Gross [83]), one would expect that occlusion of this artery would produce bradycardia, nodal rhythm, various degrees of auriculoventricular heart block and auricular fibrillation, flutter or tachycardia, and that the occurrence of these complications would be infrequent with closure of the left coronary artery which supplies the auricles in 20 to 40 per cent of cases and the A–V node rarely. Yet all these arrhythmias, except complete heart block, occurred as often with occlusion of the left as the right artery. When heart block was present, the right coronary artery was almost always

involved, both in our cases and in those reported in the literature.[44, 68] In the occasional cases in which thrombosis of the left anterior descending artery was associated with heart block, it is possible that this vessel and not the right coronary supplied the junctional tissues or that the right coronary artery was already markedly sclerotic and stenosed and that the greater part of the circulation to the junctional tissues had been supplied by anastomotic vessels from the left coronary artery.

In recent discussions, the relationship of *heart failure* to arrhythmias, particularly auricular fibrillation, has assumed a prominent place. Luten [84, 85] stated that the tachycardia which occurs in heart failure is a compensatory mechanism and that auricular fibrillation, when it occurs, usually is secondary to and not the cause of heart failure. He believes that in the presence of auricular damage, dilatation and stretching of the auricular wall from increased intraauricular pressure in ventricular insufficiency is the predisposing factor in the production of auricular fibrillation. The same explanation could be applied to auricular flutter and auricular tachycardia. Vaquez [86] and Nahum and Hoff [87] also thought that auricular distention was responsible for the frequent association of auricular fibrillation and heart failure.

In a number of cases we have been able to study the validity of this mechanism of heart failure and auricular distention in coronary thrombosis (table 3). We have already found [69] that heart failure occurs in the

TABLE III

The Relation of Auricular Fibrillation to Heart Failure in Coronary Thrombosis

Case	Day of Attack	Rhythm	Ventricular Rate	Circulation Time—Sec.	Venous Pressure —cm.	Vital Capacity —c.c.	Clinical Heart Failure	
							Left	Right
1.	1	Aur. fib.	110	15	6	2700	0	0
	3	R.S.R.	80	13	5	2600	0	0
2.	2	Aur. fib.	110	31	12	1750	+++	++
	14	Aur. fib.	100	22	4.5	2300	+	0
3.	1	R.S.R.	75	17		2700	±	0
	12	R.S.R.	75	23		2800	+	0
	21	Aur. fib.	150	34			+++	+
	22	R.S.R.	85	29		1600	++	+

majority of patients with coronary thrombosis. Infarction and failure of the ventricles place a strain on the auricles which dilate. Auricular dilatation may be seen experimentally and is also suggested by the appearance of large P-waves in the electrocardiogram.[88] While most of our cases of auricular fibrillation and paroxysmal tachycardia were associated with heart failure, fibrillation occasionally occurred when there was no clinical evidence

of failure or when objective tests, such as the circulation time, indicated only a mild degree (Case 1). Sometimes, auricular fibrillation persisted when heart failure had entirely or largely disappeared (Case 2). Yet, in several instances, even with rapid ventricular rate it spontaneously remitted to normal rhythm in the presence of unchanged or increasing failure (Case 3). This was true in eight of the nine cases with paroxysmal tachycardia. One patient who entered the hospital with definite failure following coronary occlusion developed auricular fibrillation with rapid ventricular rate on the fourth day. During the next 24 hours the failure became advanced and the patient died the following day, yet the arrhythmia spontaneously gave way to sinus tachycardia the day before death. In addition, many of our severest cases of heart failure were associated with regular sinus rhythm. Hence we believe that although heart failure with dilatation of the auricles probably exerts an important influence in the initiation of arrhythmias in coronary thrombosis, many other factors come into play.

Since thrombosis always occurs in patients with diseased coronary vessels, chronic pathological changes which may be significant in the onset of an arrhythmia are usually coexistent. Further defective nutrition of this diseased heart muscle consequent on infarction may produce irregularities. Because of the hypertension so commonly found in coronary thrombosis, especially in patients with arrhythmias, myocardial fibrosis is particularly marked. Moreover, hypertension itself may predispose to arrhythmias. Coronary artery disease alone has not been considered a significant etiological factor in the permanent type of auricular fibrillation in non-valvular heart disease, but rather hypertension.[32, 75] Brown [75] found that in coronary artery disease auricular fibrillation was rare unless preceding hypertension was present. No specific pathologic lesion has been found in the auricles even in permanent fibrillation and frequently, no lesion at all.[32, 74, 89] It seems reasonable to assume that such is the case following acute coronary occlusion.

Ventricular tachycardia deserves special comment. Its rarity in coronary thrombosis in man is in marked contrast to its frequency in experimental coronary ligation [6-12] Experiments in dogs have emphasized unduly the significance of this arrhythmia with the result that single case reports [46-59] have been considered worthy of publication, thus centering attention on the association of coronary artery thrombosis with ventricular tachycardia. Actually, it is one of the rarest of the arrhythmias and occurs only once in several hundred cases. It should be remembered that experimental ligation produces a sudden change in an animal with normal arteries while in man the occlusion caused by coronary thrombosis is gradual and accompanied by compensatory anastomoses produced by previously sclerotic vessels. In the majority of instances in which ventricular tachycardia has been observed in coronary thrombosis it has followed administration of digitalis.[42, 49, 82, 90, 91] This is doubtless more than a coincidence since digitalis increases the irri-

tability of the heart muscle and in coronary thrombosis where irritability is already great, it may act as a predisposing factor. In fact, during the past few years since the danger of digitalis in infarction has been recognized and the drug withheld, ventricular tachycardia has become very uncommon. However, as Gallavardin and Froment [61, 62] have suggested, when ventricular tachycardia occurs in a middle-aged patient, coronary artery thrombosis is to be considered a likely diagnosis.

We have already stated that the majority of arrhythmias appear within the first three days of the coronary occlusion and spontaneously remit within 24 to 36 hours. This early appearance of the irregularities can probably be attributed to the fact that in the first few days the pathological and physiological changes are most acute and their ephemeral character probably depends on the subsidence of the acute process in the heart muscle and the improvement in the general circulation of the body. Disappearance of edema adjacent to the infarcted area which may be the site of origin of arrhythmia, may lead to rapid resumption of normal rhythm. The enlargement of anastomotic channels already present or the development of new ones is another possible factor in the short duration of the arrhythmias. It has been suggested [38, 44, 68] that in heart block the diffuse anastomosis around the A–V node between the left and right coronary arteries [92, 94] may prevent the development of the arrhythmia or prevent it from becoming permanent.

Prognosis

Diversity of opinion exists concerning the prognosis of auricular fibrillation in coronary thrombosis. Christian [17] states: "In my experience those patients developing fibrillation have shown a better prognosis than others." Parkinson and Campbell [74] maintain that auricular fibrillation has no effect on the clinical course and Levine [22] found no influence on the mortality rate. Yet Bedford [95] states that auricular fibrillation adds to the risk of an attack, although it does not preclude recovery, and seven of Howard's [27] 10 patients with auricular fibrillation died. Padilla and Cossio [96] also believe that it is of prognostic significance. Half of our cases with auricular fibrillation ended fatally, a mortality rate more than double that in patients with normal rhythm.

Auricular fibrillation occurred most frequently in severely ill patients with an advanced degree of heart failure. How significant the fibrillation itself was in the outcome of the attack is problematic since the irregularity usually lasted but a short time and in half the fatal cases death occurred some time after the cessation of arrhythmia. Furthermore, as we have already pointed out, the transitory fibrillation also occurred in patients with little or no heart failure whose condition steadily improved. It would seem, then, that the importance of auricular fibrillation as a prognostic factor is determined largely by the degree of shock and heart failure present at the

time. However, if a rapid ventricular rate persists, the arrhythmia itself becomes a factor in the fatal issue by increasing the degree of shock and failure. In previous reports [69, 97] we expressed the opinion that heart block alone of the arrhythmias altered the prognosis of the attack; further experience with a larger series makes it apparent that auricular fibrillation, too, is of serious import.

The conclusions regarding auricular fibrillation also apply to auricular flutter. Yet, in spite of a rapid ventricular rate comparable to that in auricular fibrillation, auricular and nodal paroxysmal tachycardia did not affect the outcome of an attack adversely. Only two of our eight patients died. Although the number of cases is too small to generalize it is probable that the low mortality is explained by the fact that the arrhythmia in seven of the eight patients was of short duration.

Premature beats even when multiple were not of importance unless both auricular and ventricular beats occurred together. But here again, the number of cases is too small to permit conclusions to be drawn. However, most authors have found premature beats of little importance although a few [12, 66, 103] speak of the inherent danger of multiple ventricular premature beats developing into ventricular tachycardia or fibrillation. Such an association occurred only once in our series.

Complete heart block has been recognized as a very serious irregularity. Karsner [16] states that it usually ends fatally, a fact borne out by the high mortality rate in most of the reported cases and in our series in which it was 80 per cent. However, in occasional instances, recovery does take place, and indeed Schwartz [44] states that 11 of his 15 cases with Stokes-Adams syndrome due to complete heart block survived the acute attack of thrombosis. The high mortality in complete heart block is undoubtedly associated with the marked bradycardia. In three of our four fatal cases the rate remained below 40 until death. In contradistinction, in both Levine's [22] and our own series, partial heart block had no effect on the prognosis. In our three cases the ventricular rate was 50 or more, no Stokes-Adams symptoms occurred and none died.

Since only one case with very fleeting ventricular tachycardia was encountered in our entire series, we are unable to discuss this arrhythmia from personal experience. It has generally been considered a very serious complication. About three-fourths of the cases of coronary artery thrombosis with ventricular tachycardia reported in the literature [46–59] ended fatally. The gravity of this arrhythmia may lie in the fact that it usually occurs in patients with severely damaged hearts and large infarcts and that it tends to remain more persistent than other forms of paroxysmal tachycardia.

Treatment

Since arrhythmias in coronary artery thrombosis are usually transitory and remit spontaneously, specific therapy, such as *digitalis administration*

advocated by some authors [13, 24] is not routinely necessary. The general measures employed in coronary thrombosis will usually suffice. These measures which we have fully described in previous articles [97-100] include meticulous care of the diet, absolute quiet and sedation, particularly with morphine. During the first few days the diet consists of small portions of soft food totalling several hundred calories during the day. Such a regime reduces the work of the heart and avoids gastro-cardiac reflexes. If the condition of the patient improves, the caloric intake is rapidly raised to 800 calories and is maintained at this amount for two or three weeks or more. Fluids are restricted to 1200 c.c. during this period. The first week or two visitors are not allowed and the patient is fed by the attendant. Under this treatment pain usually disappears after the first or second day and the patient is comfortable. When heart failure, frequently present soon after the attack, increases, diuretics such as mercupurin are employed and oxygen if there is cyanosis or dyspnea. We believe, as do most authors,[22, 42, 101, 102] that digitalis is contraindicated in the first weeks following coronary artery thrombosis. It not only increases the work of the heart but there is a great deal of evidence [42, 90, 102] that it initiates or prolongs arrhythmias, particularly ventricular tachycardia and auricular fibrillation, when infarction exists. It is possible that the rarity of ventricular tachycardia in our series was associated with the avoidance of this drug. However, in the occasional cases in which auricular fibrillation with rapid ventricular rate persists and increasing heart failure or shock is present, the administration of digitalis may be necessary. Usually one may wait 24 to 36 hours before giving the drug but this will depend on the individual case.

Although we avoided the use of digitalis as a rule, six patients with auricular fibrillation or flutter did receive the drug through error. In three, it was given after the onset of the arrhythmia; two of these died suddenly before the arrhythmia ceased and in the other, fibrillation became permanent. The remaining three cases received digitalis before the onset of the irregularity and one died. In these cases, therefore, digitalis did not prevent or abolish the arrhythmia.

Since Levine [22, 48, 60, 63] advocated *quinidine* for ventricular tachycardia in coronary thrombosis its use has become very common [42, 62, 91]; in fact, the prophylactic administration of this drug soon after the onset of the attack to prevent ventricular tachycardia and fibrillation has been advised [60, 66, 103] particularly if premature beats are present. However, the rarity of ventricular tachycardia in coronary artery thrombosis makes it seem inadvisable to give routinely a drug which may be dangerous. Even if ventricular tachycardia should set in, it may be transitory, as in our single case, or may respond to morphine. If, on the other hand, it persists and heart failure increases, quinidine should be given in sufficient dosage.[60] The intravenous administration should be employed only if the condition is urgent, when it should be given cautiously, that is, slowly and well diluted.[63]

Auricular and nodal tachycardia almost always remit spontaneously or after the use of morphine. However, if the rapid ventricular rate is associated with increasing failure, in spite of the morphine, quinidine or digitalis should be given. In one of our cases nodal tachycardia ceased after 54 grains of quinidine; however, the patient died of a cerebral embolus four days later.

Levine [22] and Schwartz [44] have advised the use of *adrenalin* when the Stokes-Adams syndrome complicates complete heart block. In spite of the danger of adrenalin in coronary artery thrombosis, this drug should be tried cautiously, because this condition is so serious and without treatment frequently ends fatally. Schwartz reported good results in his cases.

Summary

In this paper we have presented the conclusions drawn from our study of the arrhythmias occurring in 300 cases of coronary artery thrombosis and reviewed the literature pertaining to the subject. Women were almost twice as prone as men to cardiac irregularities.

All types of irregularities were present. Premature beats found in one-fourth of the patients were the most common, but were of little prognostic significance. Other arrhythmias occurred 46 times in 42 patients (14 per cent). Of these, auricular fibrillation comprised one-half. Ventricular tachycardia was rare, occurring only once. There were eight cases of auricular or nodal tachycardia, five of complete and three of partial heart block. In some instances several arrhythmias developed in the same patient.

The arrhythmias may occur at any time but they usually appeared during the first three days following an occlusion. With the exception of nodal rhythm and heart block which may last one to two weeks, they were transitory, more than half remitting spontaneously within 24 hours.

The mortality rate of the patients with a significant arrhythmia, that is, any arrhythmia other than premature beats, was 39 per cent, while for those with regular sinus rhythm it was 22 per cent. This high mortality rate was attributed to the underlying cardiac enlargement, heart failure and hypertension. Half the deaths occurred after the cessation of the arrhythmia. Only very rarely was the arrhythmia itself the cause of death. Half the patients with auricular fibrillation and flutter, and four-fifths of those with complete heart block died, whereas the patients with paroxysmal tachycardia, nodal rhythm and partial heart block usually survived.

The cardiac rate, whether or not the rhythm was regular, was a very significant factor in the outcome of an attack. If the ventricular rate was above 120 or below 40 beats per minute the outlook was poor; when a rate between 60 and 100 was maintained, the patient almost always recovered.

An arrhythmia may be the first and only sign of coronary artery thrombosis, pain being absent or minimal; in fact, the sudden onset of an arrhythmia should suggest the diagnosis of coronary occlusion. On the other hand,

an arrhythmia with rapid ventricular rate may lead to shock and heart failure which may simulate another coronary occlusion.

A number of factors probably play a rôle in the initiation of the arrhythmias: heart failure with its associated dilatation of the auricles, anoxemia of the myocardium, nutritional or metabolic disturbances and impulses or reflexes originating in and around the infarcted area. Indeed, it is surprising that arrhythmias are not more frequent. Their relative rarity is probably the result of the copious anastomoses throughout the heart, particularly around the A–V node and septum.

Coronary thrombosis is rare when auricular fibrillation is present.

Heart block alone was associated with a specific anatomical lesion in the heart, that is, posterior wall infarction due to right coronary artery occlusion. In the other arrhythmias both the left and right coronary arteries and both the anterior and posterior surfaces of the left ventricle, were involved with equal frequency. The site of acute infarction or chronic fibrosis does not determine the type of cardiac irregularity.

Because the arrhythmias usually remitted spontaneously after a short period we considered specific treatment unnecessary, either prophylactically or after the onset. In fact, digitalis and quinidine are considered dangerous in the treatment of coronary artery thrombosis since they may actually initiate arrhythmias. The rarity of ventricular tachycardia in our series may be due to the fact that digitalis was not used routinely. Only when a persistent arrhythmia produces severe shock or increasing heart failure should they be given. At the onset of an arrhythmia morphine may be administered liberally. Adrenalin should be used in heart block but only when a severe Stokes-Adams syndrome occurs.

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THE SURGICAL TREATMENT OF PEPTIC ULCER*

By Irvin Abell, *Louisville, Kentucky*

Since Billroth, following his successful removal of a carcinoma by pylorectomy in 1881, directed his efforts to the cure of peptic ulcer by surgical measures, a voluminous literature, both medical and surgical, has been accumulated. It is now the consensus of opinion that the problem of the treatment of peptic ulcer is primarily a medical one, assuming surgical significance only with its complications, sequelae and intractable chronicity. The aim of treatment has been to secure a healing of the ulcer or its eradication with a correction of the pathological defects caused by it, together with the institution of such measures as in the light of knowledge and experience are believed to be of value in the prevention of recurrence. In the many types of operations that have been employed, the underlying considerations have been to bring about, as far as possible, a restoration of physiological function, free drainage of the stomach and a partial neutralization of stomach acids by intestinal alkalies.

The occurrence of perforations, bleeding, and malignant degeneration in ulcers left behind, has led to the conviction of the desirability of destroying or removing the ulcer or ulcers in addition to meeting these indications. The wide variation in the degree and character of the lesions encountered in peptic ulcer is such that no single operation suffices to meet the indications in all cases. The attainment of success in its surgical treatment is largely dependent upon three factors: choice of operation, selection of cases for operation, and efficient pre- and post-operative medical management.

For the purpose of discussion, the operative procedures with which we have had personal experience may be classified as conservative and radical. The conservative operations comprised, (*a*) local excision with cautery or knife followed by suture; (*b*) local excision plus gastro-enterostomy or pyloroplasty, (*c*) gastro-enterostomy or pyloroplasty alone. The radical operations consisted in the removal of the ulcer-bearing area by the Billroth I, Billroth II, Polya modification, or sleeve resection methods.

In making a choice of the type of operation to be employed in a given case primary mortality and end results must be the chief considerations. It is obvious that where resistance and vitality have been lowered by long continued disease, marked pyloric obstruction with dehydration and toxemia, inadequate nourishment or continued blood loss, the pre-operative administration of fluids, glucose and blood transfusions are essential in the preparation of the patient for operation, and it is equally obvious that the safety of the patient will be enhanced by the selection of the simplest operation compatible with the correction or alleviation of the pathologic condition

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presented. While the roentgen-ray is an invaluable aid in diagnosis, the extent of the local lesion will be revealed by ocular inspection only. Quiescent ulcers will permit safer attack than those showing evidence of activity.

Perforation into the free cavity or into adjacent viscera; fixation of the duodenum, pylorus and stomach; the presence of inflammatory exudate, recent or calloused; obstruction due to cicatricial contraction; exudative or massive adhesions; location and number of ulcers in varying combinations, present problems that are most satisfactorily solved by the selection of that operation best suited to the given case. The clinical observation that 90 per cent of gastric ulcers occur at or near the pylorus and along the lesser curvature led Rodman to advocate the resection of the ulcer-bearing area when dealing with ulcers in this location. Time and experience have demonstrated the wisdom of this procedure particularly when the ulcers are of the calloused variety. Finally a consideration influencing the choice of operation is the efficacy of large resections in the reduction of gastric acidity. The observation that following resection of the ulcer-bearing area of the stomach there is a lowering of gastric acidity, and further, that freedom from recurrence is the rule (to which, however, there are exceptions), has led to the assumption in some quarters that where there is no acid there will be no ulcer. On this hypothesis Finsterer and his followers have practiced the ablation of the acid-bearing portion of the stomach regardless of whether the ulcer be duodenal or gastric, with the avowed intention of producing anacidity. We have had no experience with such massive resections other than when necessitated by the location and character of the ulcer, believing the magnitude and extent of the operation to be prohibitive when compared with the favorable results obtained by simpler and less dangerous procedures. Furthermore, the presence of hydrochloric acid is essential to the proper physiological action of the stomach and its continued absence, howsoever produced, may be the forerunner of serious secondary disease.

The selection of the type of operation to be employed is, and should be, the concern of the surgeon: the selection of the case for operation should be the joint concern of the internist and the surgeon. While unanimity of opinion is not yet to be obtained, accumulated experience and knowledge permit fairly definite indications for operative treatment. The three indications upon which all agree are: perforation, hemorrhage, and obstruction.

Immediate closure of an acute perforation is the essential indication. Approximately 80 per cent of the acute perforations of duodenal ulcers occur on the anterior wall, and 90 per cent of the acute perforations of stomach ulcers occur on the lesser curvature of the prepyloric portion: perforation on the posterior wall is frequently sealed by adhesion of adjacent structures. Closure of the opening with superimposed layers of Lembert sutures and an omental fat graft suffices not only to control leakage but in a goodly percentage to secure healing of the ulcer as well. The employment of additional measures, such as excision or cauterization of the ulcer, py-

loroplasty, gastro-enterostomy or resection of stomach will depend upon the extent, character, and location of the local lesion and the general condition of the patient. The prime consideration in such catastrophes is the saving of life: this is accomplished by the stoppage of the leak. It may be stated as a general rule that the greatest safety to the greatest number prohibits doing more, yet, in the presence of marked pyloric or duodenal obstruction, granting that the condition of the patient permits, a pyloroplasty or gastro-enterostomy may be done with reasonable safety, thus giving assurance of permanent relief and obviating a second operation. If the perforation occurs in a calloused ulcer on the lesser curvature, the infiltration surrounding the ulcer may not only prevent suture but may arouse the suspicion of malignancy as well, in which event excision or gastric resection will be indicated, as the condition of the patient and the judgment of the operator dictate. Perforations in which more or less successful efforts at closure have been made by nature are observed in three clinical groups: one, rather extensive epigastric peritonitis with subhepatic or subphrenic abscess; two, localized peritonitis with recent inflammatory exudate matting together structures adjacent to the perforation; and, three, chronic perforations in which the acute inflammatory phenomena have disappeared and the perforations remain sealed by close adherence of adjacent tissues. In the first two groups, the perforation itself, surrounded and sealed by acutely inflamed tissues, will neither demand attention nor permit surgical attack, the operative treatment consisting in the first group of drainage of the purulent deposits and in the second of gastro-enterostomy. In the third group the location of ulcer and the nature of the structures to which it has adhered will determine the nature and extent of the operation.

Hemorrhage in both gastric and duodenal ulcers occurs in approximately 25 per cent of all cases, appearing usually in one of three forms: (1) More or less constant seepage sufficient to produce anemia; (2) single or recurring hemorrhages of appreciable amount as hematemesis or melena and (3) massive bleeding, which immediately threatens the life of the patient. Ulcers that show constant seepage and recurring hemorrhage of appreciable amount which continues in spite of appropriate medical treatment should be subjected to operation. The type of operation employed should include the destruction of the ulcer, since such ulcers, when treated by conservative operations which do not include their eradication, show in many instances a definite tendency to further bleeding. The treatment which we have employed for massive hemorrhage consists of rest in bed; physiologic rest of the stomach; fluids and nutrition in the form of glucose administered by rectum, subcutaneously, and intravenously; the exhibition of coagulants, chiefly fibrogen by mouth and subcutaneously; and whole blood transfusions. Under this regime the bleeding as a rule will cease, permitting of further study of the patient and a decision for or against operation based upon the associated symptoms, history and laboratory findings. Occasionally a case

will be met in which such measures fail, in which the necessity of controlling the bleeding becomes an indication for immediate operation.

The patients with duodenal ulcers that we have selected for operation have presented one or more of four conditions: (1) Perforation, both acute and chronic; (2) repeated or long continued hemorrhage; (3) pyloric obstruction; (4) and marked chronicity. A single massive hemorrhage is not regarded as an indication for operation; and in such cases in the absence of the remaining conditions the chance for healing under medical treatment should be afforded until further bleeding or chronicity demonstrates its futility. Chronicity in spite of appropriate medical treatment is accepted as a failure of the latter and an indication for operation. For some unexplained reason duodenal ulcers do not show a tendency to malignant degeneration; hence it has been argued that chronicity alone does not justify resort to operation. The danger of perforation, the menace of hemorrhage, the possibility of obstruction and the continued discomfort produced by the chronic ulcer which proves resistant to an intelligently planned medical treatment afford sufficient grounds to negate this assumption.

The types of operation which we have employed in the treatment of duodenal ulcer are: Excision alone; gastro-enterostomy alone; excision or cautery destruction of the ulcer combined with gastro-enterostomy or pyloroplasty; and resection of the pylorus and duodenum. Resection of the ulcer alone was tried in a small series of cases and abandoned since three patients so treated showed recurrence within a year. Excision of the ulcer with a pyloroplasty, Finney or modified Mikuliez, has been employed for ulcers situated on the anterior wall near the pylorus, showing a minimal amount of duodenal distortion. For the satisfactory performance of this operation it is essential that the pylorus and duodenum be readily mobilized so as to afford opportunity for the necessary manipulation. In the cases conforming to these limitations it has proved a satisfactory procedure.

With increasing experience gastro-enterostomy is less frequently employed alone as the treatment of choice in duodenal ulcer. The destruction of duodenal ulcers is not an imperative indication, but when local conditions make this a feasible and reasonably safe procedure it is advisable in that it at once gets rid of the ulcer, avoiding dependence on a slow healing process, and obviates the possibility of subsequent bleeding and perforation. The eradication of the ulcer is preferably accomplished with the cautery after the method of Balfour. With this technic the bleeding and operative trauma are decidedly less and the destruction of the ulcer just as certain. The cautery wound is closed with Lembert sutures and covered with an omental fat graft, after which a posterior gastro-enterostomy is done. This conservative procedure will meet the indications in the majority of simple duodenal ulcers and the excellent results obtained place the burden of proof upon advocates of other methods to show just cause for such advocacy.

In the presence of obstruction due to cicatrization in the duodenum and pylorus dependent upon ulcer of the duodenum, gastro-enterostomy alone

affords beneficient results; the greater the obstruction the more certain and more complete the relief. Gastro-enterostomy alone is also to be considered where marked periduodenal inflammation has anchored the gut to the liver, and in those cases where age, lowered vitality or obesity contraindicate any direct procedure. When the ulcers are multiple, and they are in from 5 to 6 per cent of cases; when situated on the posterior wall, difficult of access and so calloused as to render healing difficult; and when, so situated, the ulcer has perforated into the head of the pancreas with fixation of duodenum and pylorus to the latter organ, we have come to the practice of resection of the duodenum and pylorus. Ulcers presenting such complicating lesions do not lend themselves to cautery destruction or to excision with pyloroplasty. Our experience with gastro-enterostomy alone in such cases has been disappointing in that persistent gastric discomfort, recurrent bleeding, pancreatitis and pancreatic malignancy have been noted. It is true that the radical operation carries a graver operative risk, but this is justified by the greater assurance of relief.

The indications for the institution of surgical measures in the treatment of gastric ulcers comprise those which apply to duodenal ulcers, namely, perforation, hemorrhage, obstruction and chronicity, to which must be added the danger of malignant degeneration. While malignancy does not become engrafted on chronic ulcer with the frequency which some authors have stated, personal observation has afforded conviction of its occurrence. Patients with frank cancer at the time of examination have given ulcer histories of long duration: patients upon whom in our earlier experience we had done gastro-enterostomy alone for chronic gastric ulcer have returned years later with gastric carcinoma. This common observation of the tendency of chronic gastric ulcer to undergo malignant transformation would seem to render imperative the destruction or removal of the ulcers in the course of operations undertaken for their relief. The operations with which we have had experience are gastro-enterostomy alone; excision of ulcer alone; cauterization or excision combined with gastro-enterostomy; sleeve resection of the pars media, and resection of the pylorus, antrum, and such part of the pars media as may be necessary to include the ulcer-bearing area. The above mentioned observation of the occurrence of carcinoma in chronic ulcer treated by gastro-enterostomy alone has led us to abandon such conservatism and in the cases selected for this procedure to supplement it with cauterization or excision of the ulcer. In four patients presenting chronic saddle ulcer of the lesser curvature, pars media, a sleeve resection was done. In two of these recurrence was noted and relief obtained by a subsequent gastro-enterostomy. The cases to which the combined procedure of excision or cauterization combined with gastro-enterostomy is applicable are those in which small, resectable ulcers are situated on the lesser curvature, or in the pars media; and also all ulcers situated high on the lesser curvature or posterior wall. Ulcers of the lesser curvature

showing marked inflammatory deposit are best treated by sleeve resection with a gastro-enterostomy, or by pyloric resection, since the defect left by excision or cauterization is such as to render accurate suturing difficult and to produce marked distortion and deformity. Ulcers with a crater of one centimeter or less in diameter are rarely malignant, and are susceptible of conservative treatment; when the craters present larger diameters, the presence of malignancy is to be considered as possible, and unless one feels confident of his ability to distinguish by ocular inspection between simple chronic ulcer and ulcerated carcinoma, or ulcer with beginning carcinoma, the patient should be given the benefit of the doubt and radical treatment employed. Ninety per cent of gastric ulcers occur on the lesser curvature and posterior wall at the pyloric end of the stomach, the ulcer-bearing area of Rodman. The presence of inflammatory deposit in the stomach wall around the margin of the ulcer, the presence of perigastric adhesions or of sealed perforation into the liver, pancreas or gastro-hepatic omentum, and the size of the stomach at this point make difficult, if not impossible, the employment of conservative excision or cauterization. The probability of failure of healing with a continuation of symptoms and the possibility of perforation, bleeding and malignant transformation, if gastro-enterostomy alone is done, have led to the rather universal acceptance of pyloric resection as the operation of choice in such cases. The Billroth I gives a nearer approach to physiological restoration, when local conditions are such that it can be carried out. In the wider resections the Polya modification of the Billroth II has satisfactorily met the indication.

A proper selection of patients for operation and the use of good judgment in the choice of operation for the given patient combined with dietary and medical supervision for at least one year following operation, offer the sufferer from intractable peptic ulcer, its complications and sequelae an excellent chance for relief. Peptic ulcer may recur after any type of operation, being located at the former suture line or in new locations in the stomach and duodenum, or in the jejunum at or below the site of anastomosis with the stomach. Fortunately, recurrent ulcer is observed in but a small percentage of cases. The cause for recurrence of ulcer is as elusive as that for its primary appearance. Other sources of failure are to be found in faulty operative technic; in leaving behind an infected gall-bladder or diseased appendix; in activation of an unremoved ulcer; in overlooking distant foci of infection; in the resumption of a faulty diet.

Finally, it should be borne in mind that in the vast majority of patients presenting gastric symptoms, the latter are due to causes extrinsic to the gastric tract. Granting the coincidental occurrence of peptic ulcer in such a patient, its treatment is doomed to complete or partial failure in so far as securing freedom from symptoms is concerned, unless the extra-gastric causes of dyspepsia can be eliminated.

REACTION AND SPECIFIC GRAVITY OF THE URINE IN RELATION TO NEPHRITIS (A STUDY OF TEN THOUSAND URINALYSES) *

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Introduction

A statistical analysis of over 10,000 urine specimens is presented. Special attention was given to the specific gravity of urines in relation to their reaction and to pathological findings.

Some significant correlations have been discovered which may have important clinical applications, especially with reference to the management of nephritis and allied diseases.

The data involved in this report represent consecutive urinalyses performed in approximately a year's time in an active general hospital. The bulk of the urinalyses were single morning specimens from hospital patients. A small fraction were 24 hour specimens. Less than half were single specimens from out-patients.

The specimens from the hospital wards came from approximately 2,270 patients, about two-thirds of whom were surgical cases. The series therefore represents an average of between two and three urinalyses per patient. The great majority of specimens were from males, an almost negligible number being from a small female ward of the hospital.

A fraction of the urine specimens was obtained from persons in normal health. The majority of the specimens were from patients having a large variety of general medical and surgical disabilities requiring hospital treatment.

In view of the fact that acid urines may become alkaline on standing due to bacterial action, all twenty-four hour specimens were preserved with a crystal of thymol. Single morning specimens and out-patient specimens were examined promptly after their arrival in the laboratory. The number of cases which may have had alkaline urine due to bladder retention was insignificant when compared to the large number of specimens involved in this study.

Data and Experimental Work

It is generally held that the normal human urine is acid in reaction. This is stated by all authorities on physiological chemistry, and is undoubtedly true. Of the urine specimens involved in this study 87.4 per cent were found to be acid.

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The urine specimens, from which the data presented herewith were obtained, were carefully tested for reaction with good quality red and blue litmus paper and recorded as alkaline, neutral or acid. The specific gravities were carefully determined and recorded.

Of 10,155 urinalyses it was found that 319 specimens were neutral, 961 alkaline and 8,875 acid (table 1).

TABLE I

	Acid	Neutral	Alkaline
Number of specimens	8,875	319	961
Per cent of total specimens	87.4	3.1	9.5
Mean specific gravity	1.020	1.014	1.013
Probable error of mean	±0.00005	±0.00025	±0.00015
Standard deviation	±0.0047	±0.0046	±0.0048
Range of specific gravity	1.015–1.024	1.010–1.019	1.008–1.018
Pathological specimens	448	29	106
Per cent pathological	5%	9%	11%
Output of solids per liter	52 gm.	36.4 gm.	33.8 gm.

The average specific gravity of the neutral specimens was 1.0141, of the alkaline group 1.0127, and of the acid group 1.0196. The distribution curve of the specific gravity in each of these groups is shown in chart 1.

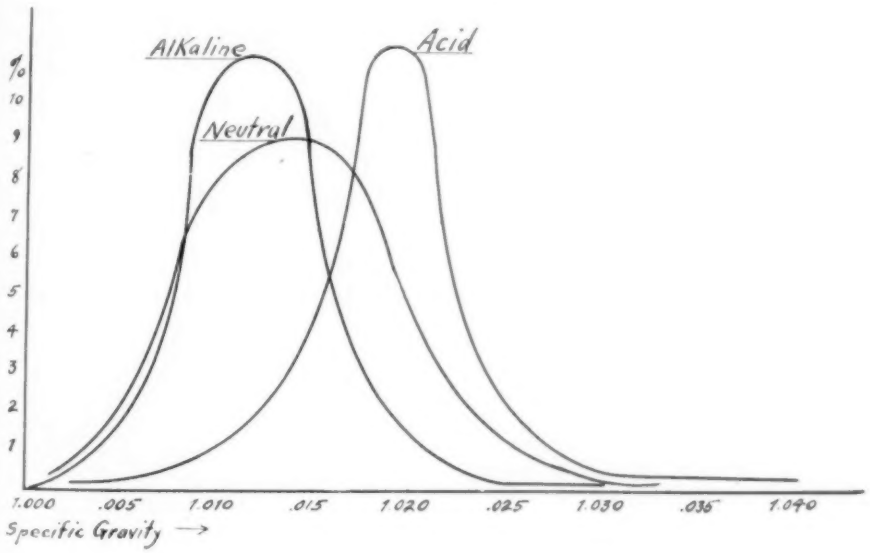

CHART I. Distribution of 10,000 urinalyses.

There was a difference between the neutral and alkaline averages of 0.0014. The standard error of the difference was ± .00029, making the difference 4.8 times the standard error of the difference.

The difference between the means of neutral and acid groups was 0.0055.

The standard error of the difference was $\pm$ .000255. This gave a difference 21.5 times the standard error of the difference.

Between the acid and the alkaline groups there was a difference of 0.0069 with a standard error of $\pm$ .000158. Thus the difference is 43.6 times the standard error of the difference.

The above figures are highly significant. They show definitely that there is a correlation between the specific gravity and the reaction of the urine. Statistically speaking, when the difference between the means of two series is over two times the standard error of the difference it is regarded as definite evidence of significant difference, and not due to chance.

It has been found that the specific gravity of acid urines is higher than that of neutral urines, and that of neutral urines higher than the specific gravity of alkaline urines. It has been shown definitely that these differences are not accidental, but that they are due to definite factors causing a correlation between reaction and specific gravity of the urine.

Long's coefficient or Häser's method [1] may be used to determine the output of urinary waste products from the specific gravity of the urine. This is done as follows: Multiply the last two figures of the specific gravity by the coefficient of 2.6. This gives the total solids in one liter of urine. To determine the total solids in the 24-hour specimen multiply the above product by the volume of the specimen in cubic centimeters and divide by 1,000. For example let the specific gravity of the 24-hour specimen be 1.012, the amount 1,200 c.c., then:

$$\frac{12 \times 2.6 \times 1200}{1000} = 37.4 \text{ gm.}$$

If we assume that the average output of urine is 1,000 c.c. for each of the groups (acid, alkaline and neutral), and apply Long's formula, we find that there will be an average of 52 grams of solid waste matter excreted in the acid group, 36.4 grams in the neutral group and 33.8 grams in the alkaline group.

It may be true in some cases when the urine is alkaline and has a low specific gravity there will be a compensatory increase in the urinary volume. The average 24-hour volume for a series of alkaline urines was 2,066 c.c. For a series of acid urines it was 1,611 c.c. Applying Long's coefficient to these average values we find that the excretion of solids would be:

AVERAGE VALUES

	Volume	Specific Gravity	Total Solids
Acid	1,611 c.c.	1.020	83.8 gm.
Alkaline	2,066	1.013	69.8
Difference	—	—	14.0 gm.

Thus it is shown in this series that the average amount of excretory solids of the urine is greater in the acid series than in the alkaline. It must be

remembered that here we are dealing with averages. The values in individual specimens may vary greatly.

This indicates that the ability of the kidney to excrete solids and to concentrate the urine is greater when the urine is acid.

It has been common practice for the physician to prescribe alkalies in the treatment of nephritis. Empirical improvement in such cases has unquestionably occurred following alkaline medication. In view of this fact it was determined to study the effect of an alkaline medium on the formed elements of pathological urines. In order to do this the following experiment was performed in vitro.

Acid urines containing casts and usually other abnormal findings, as albumin, red and white blood cells, were alkalinized with sodium hydroxide. Sodium hydroxide (10 per cent solution) was added drop by drop to the individual specimens until the specimens gave a permanent pink color to phenolphthalein. This gave a pH about 8.4. The alkalinized urine specimens, containing casts, were then incubated at 37.5° C. in a water bath for various periods of time. The findings were as follows:

After three hour incubation the casts were partially dissolved. All casts dissolved in the incubated alkaline urines in four hours or more. When potassium hydroxide was used to alkalinize the acid urines in place of sodium hydroxide, the casts were just as effectively dissolved. Other formed elements, especially red blood cells, tended to disappear also but not to the same extent as casts.

Crystals were not especially studied but seemed to be increased in amount on alkalinizing the acid urines.

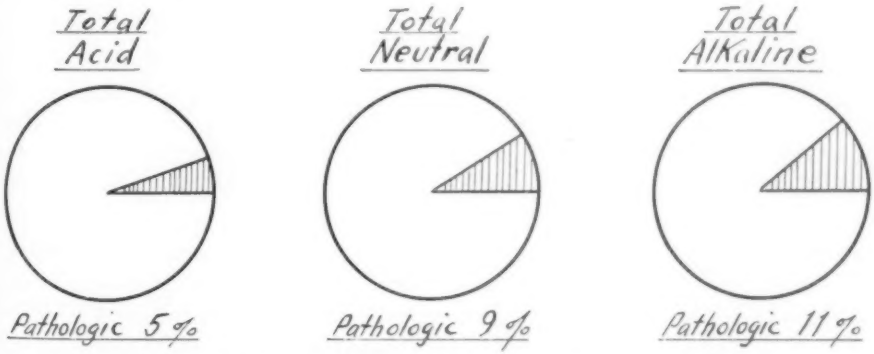

CHART II. Incidence of pathologic specimens in 10,000 urinalyses.

Further evidence that there is a correlation between kidney disease and urinary reaction has been found. As shown in table 1, 11 per cent of alkaline urines, 9 per cent of neutral urines and only 5 per cent of acid urines were pathological (chart 2). In this study, urines were listed as pathological which contained one or more of the following constituents: sugar, albumin, casts, red blood cells and pus.

TABLE II

Specimen	Specific Gravity	Sugar	Reaction	Acetone
WES 1	1.030	4%	Alkaline	Trace
ROS 2	1.025	—	Alkaline	Trace
CM 3	1.029	—	Alkaline	Trace
RJM 4	1.028	—	Alkaline	Trace
GFL 5	1.035	—	Acid	—
GFL 5a	1.026	Trace	Alkaline	Trace
HK 6	1.029	—	Alkaline	Trace

As shown in table 2 there were six urine specimens in the series which were alkaline in reaction and yet showed traces of acetone. This seemed to be a rather unusual finding and it is not explained nor understood. This phenomenon has been reported before by Schrader.[2] It seems to indicate that ketosis can exist even when there is an excess of alkaline salts in the body and urine.

DISCUSSION

The above findings do not support the practice of prolonged alkalinization for nephritis, especially in those cases where there is retention or uremia, since it appears that the ability of the kidney to excrete solids is greater when the urine is acid. However it has been common practice for the physician to prescribe alkalies in the treatment of nephritis and other urinary infections. More recently the advisability of this practice has been questioned.

Since this matter has come to our attention, we have observed a few fatal cases of uremia. The majority of the urinalyses performed on these cases were alkaline in reaction. It is natural to wonder if there is not some relationship between the poor results and the alkaline condition in such cases.

Steele [3] has recently recognized the kidney damage produced by prolonged alkaline medication. The alkalies were administered for the treatment of a patient with a gastric ulcer. On correcting the alkalosis the secretory ability of the kidneys improved. There were no clinical symptoms of alkalosis except the kidney damage, indicating that the kidneys are affected before the clinical symptoms of severe alkalosis appear.

Morgan [4] fed acid, neutral and alkaline diets to dogs in a study of calcium and phosphorus metabolism. It was concluded, among other things, that renal damage may result from the long continued use of alkaline diets. This important experimental work was discussed in an editorial in the *Journal of the American Medical Association*.[5]

Berger and Binger [6] report seven cases of alkalosis resulting from alkaline treatment of peptic ulcer. In all seven cases impaired renal function was demonstrated during alkalosis. After the alkalosis had been corrected, evidence of impaired renal function persisted in five of the seven cases, thus indicating that permanent renal damage may result from alkalosis.

In addition to the alkaline medication in cases of advanced nephritis, patients are often given an alkaline diet, consisting usually of fruit juices which further alkalinize the urine.[7, 8, 9] Fruits on being ashed yield alkaline salts predominately and are therefore alkaline ash foods.

It often happens that patients will continue alkaline self-medication after the physician has advised its discontinuance. Many people are known to take alkaline medicines for long or short periods without medical advice. It is obvious that such self-medication with alkalies is not without danger. The public is being induced to engage in alkaline self-medication by many commercial interests through various popular means of advertising.

In view of the evidence that has been accumulating on the harmful effect of prolonged alkaline medication, it is obvious that the above mentioned commercial exploitation of alkaline waters, crystals and drugs is not in the public interest. Alkaline medication, like any other medication, should be under the control of the physician. The tendency to regard alkaline self-medication as harmless should be combated by the medical profession. There is no sound reason why sodium bicarbonate should be a household remedy any more than hydrochloric acid.

In view of the above evidence that alkalies diminish the ability of the kidneys to concentrate the urine it would seem necessary to take this into consideration in performing and interpreting tests such as the Mosenthal and other kidney function tests.

In spite of the above consideration, the empirical administration of alkalies seems in some cases to have a temporarily favorable effect on nephritis. An explanation of this is suggested by some experiments, in vitro, reported above. In these experiments acid urines which contained casts were alkalinized with sodium hydroxide and after four hours' incubation, the casts were dissolved. These findings seem to justify the alkalinization of the urine in cases of nephritis with casts. The good effect of the alkalinization is probably due to the solution of casts in the kidney tubules, thus opening blocked tubules. Prolonged alkalinization would not appear necessary to accomplish this purpose, inasmuch as casts are dissolved in alkaline urines in about four hours time in vitro. Prolonged alkalinization is further contraindicated because of the danger of causing alkalosis and kidney damage as shown by various workers.

Aside from dissolving casts the administration of alkalies would seem to be contraindicated. Many investigators in recent years have shown that acid urines are bacteriostatic and in some cases even bactericidal whereas neutral and alkaline urines are not.

The Acid Regime in Treatment

The practice of giving acids, acid salts and acid ash foods seems to be indicated in cases of nephritis where there is inadequate excretion of waste products.

Acid ash foods (especially meats), have been indicted as etiological factors in the causation of nephritis, but up to the present time, there has been no generally accepted experimental work to show that the acid ash foods and the acid salts which they contain, namely sulphates, chlorides and phosphates, can cause nephritis. On the contrary, evidence has been accumulating to show that acid ash foods and acid salts have a favorable influence on nephritis and on urinary infections.

The acid foods are those which contain an acid ash—meats, game, seafood, fish, eggs, grains, cheese and some nut meats.

Thomas [10] studied the Eskimo during the MacMillan arctic expedition of 1926. He found that the Greenland Eskimo living on an exclusive acid ash diet, consisting entirely of meat, had no increased tendency to vascular or renal disease. On the other hand he found that the Labrador Eskimo who ate cooked meat with many prepared, dried and canned fruits and vegetables was very subject to both vascular and renal diseases.

In 1931 Lashmet [11] reported the treatment of nephritic edema by acid. He found that the administration of hydrochloric acid or ammonium chloride decreased the edema while neutral chlorides as sodium chloride, did not. In regard to diet, he found that an alkaline ash intake increased nephritic edema while an acid ash diet decreased the edema.

The above mentioned work of Lashmet, showing that acid medication and acid ash foods reduce nephritic edema is revolutionary to modern medical practice. In the light of evolution, however, it seems physiologically reasonable. Primitive man was nomadic and existed on acid-ash foods almost exclusively, namely; meat, fish and eggs, and later, grains. Thus the human kidney is phylogenetically adapted to excreting acid urine. This tends to class man nearer to the carnivora with acid urinary excretion than to the herbivora which excrete alkaline urine.

Tables of acid ash foods and of alkaline ash foods are available in standard works for those who are interested in this matter. Such lists are given by Sherman [12]; Hawk and Bergeim [13] and by Manville and Winchell.[14] The latter give an extensive list which was compiled from several sources.

Those who are interested in the clinical symptoms of alkalosis are referred to a recent article on "Alkali Poisoning" by Cope.[15] This author suggests the use of hydrated magnesium silicate in place of soluble alkalies for treating gastric ulcer. An abstract of this work appears in the *Journal of the American Medical Association.*[16]

Favorable reports on the treatment of urinary infections with ketogenic diets have appeared. It is suggested that perhaps the good results may have been due to the acid-ash diets used rather than to any ketone bodies that may have been formed.

The inorganic acid salts of acid-ash foods would be more effective in reducing the pH of the urine than the ketone bodies derived from lipoids. Furthermore, it is practically impossible to produce actual ketosis in non-diabetic individuals.

Ketone bodies can be present in alkaline urines. It was found that out of 961 alkaline urines, six showed a trace of acetone (table 2). The specific gravity of these specimens was unusually high for alkaline urines, indicating an unusual excretion of waste products. This phenomenon has been reported previously by Schrader.[2] No explanation is offered for this comparatively rare phenomenon. However, its occurrence suggests that acidosis and ketosis are separate and not necessarily related conditions. Ketone substances are derived from the incomplete oxidation of fats. Whereas acid substances such as the acid salts (chlorides, sulphates and phosphates) which give the urine its normal acidity, are derived from acid-ash foods of the diet and the catabolism of tissues. The specific rôle of foods in relation to the composition of the urine, has been comprehensively studied by Blatherwick.[17]

It is obvious from the foregoing that the inorganic mineral ash of foods does have a definite effect on the body chemistry and has important relationships to disease. Acid ash foods and alkaline ash foods as well as acid and alkaline medicines, deserve extensive further study in this regard.

It appears from this and other investigations that excessive alkaline intake has a deleterious effect upon the kidneys and that this effect can appear before symptoms of clinical alkalosis develop.

Summary and Conclusions

1. The ability of the kidney to excrete solids and to concentrate the urine is greater when the urine is acid than when it is alkaline or neutral.
2. Acid urines show fewer abnormal findings than alkaline and neutral urines.
3. Prolonged alkalinization of the urine apparently produces kidney damage.
4. Temporary alkalinization of the urine is apparently of service in dissolving casts and thus opening blocked kidney tubules.
5. Alkaline self-medication should be discouraged.
6. Alkaline medication, as well as acid medication, should be controlled by the physician.
7. Acid types of therapy may prove superior to alkalinization in the treatment of nephritis and its complications as well as in other urinary infections.
8. A definite correlation has been demonstrated between the reaction of the urine and its specific gravity. Acid urines generally have a higher specific gravity than alkaline or neutral specimens and therefore remove more waste products from the body.

The authors wish to acknowledge the technical assistance of Mr. Dale B. Frost, who performed the urinalyses which furnished the data for this paper.

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PROBLEMS CONNECTED WITH THE USE OF PROTAMINE–ZINC–INSULIN *

By Henry T. Ricketts, M.D., *Chicago, Illinois*

The efficacy of protamine insulin in the treatment of diabetes has been convincingly demonstrated by a number of workers [2, 3, 6, 9, 11, 12, 13, 14, 15, 18, 19] during the past year. Its superiority over the old insulin as evidenced by better control of the blood sugar, fewer reactions, reduction in the number of daily injections and often an appreciable saving in total requirement cannot be doubted.

All investigators † have recognized, however, that the slow and prolonged action to which protamine insulin owes its conspicuous advantages is also responsible for certain difficulties peculiar to its use. Its seems appropriate at this time, therefore, with the new material recently placed on the market, to report an additional series of cases with the specific purpose of redirecting attention to these problems and outlining methods of meeting them.

This study is based on experiences with the administration of protamine insulin to 26 diabetic patients. Of these, five were children. The disease was classified as severe in 12 cases, moderately severe in nine and mild in five. Of 20 patients who were first given protamine insulin in the hospital, 19 were transferred from regular insulin and one patient was treated with the protamine compound alone. In all of the hospitalized cases several determinations of the dextrose content of the blood and urine were made daily, usually before breakfast and from three to four hours after each meal. Of the six patients who were first given protamine insulin in the out-patient department, four had been taking regular insulin and two had received none.

One house physician was forced to return to regular insulin before he had become stabilized because of marked hyperglycemia alternating with severe reactions which interfered with the performance of his duties. Another patient was carried through pregnancy with protamine but was given regular insulin alone at delivery and for four weeks thereafter in the fear that the action of the former might prove too slow and inflexible to meet the rapid fluctuation in tolerance incident to parturition and lactation. With these two exceptions no patient who has started the use of the new insulin has discontinued it, and all but one have returned at frequent intervals for analyses of the blood or urine or both.

* Read in part before the Chicago Society of Internal Medicine, February 22, 1937.
From the Department of Medicine of the University of Chicago.
The author is indebted to Dr. Walford Swanson for the privilege of studying five children in the Bobs Roberts Memorial Hospital, and to Dr. Maurice Glock, Miss Vivian Iob, Miss Mabel Egan and Miss Louise Klein for numerous determinations of the blood sugar.

For the sake of simplicity the term "protamine insulin" will be used in place of protamine-zinc-insulin except where otherwise indicated.

† See especially the communication by Allen.[1]

Because of the great advantage in convenience an effort was made, successfully in all but one case,* to control the blood sugar by a single daily injection of protamine insulin given an hour or so before breakfast, either alone or in combination with a small, simultaneous dose of regular insulin. The following remarks apply particularly to this form of administration.

It should be stated in all fairness that the accompanying charts represent juvenile or relatively severe adult diabetics whose management by any method would not be easy, and they have been chosen for presentation here because they illustrate the difficulties with which any physician undertaking treatment with protamine insulin may have to contend. In the milder cases of the present series, as in other reported series, good results were obtained with much less effort.

Hyperglycemia after Meals with Normal or Low Blood Sugars during the Night

The difficulty most commonly encountered in the use of protamine insulin is that, particularly in severe cases, what appears to be the proper dose leads to marked post-prandial hyperglycemia though the blood sugar during the night or in the early morning may be normal or even subnormal (figure 1, July 21, 22; figure 2, June 5, 8; figure 3, Jan. 18, 21, 24; figures 4 and 5). Simply increasing the dose in an attempt to take care of the carbohydrate of the meals is apt to result in further hypoglycemia the following morning or before (figure 3, Jan. 18, 19, 24, 25, 26). In such a dilemma several courses are open.

(*a*) The time of administration of the protamine insulin may be pushed back to two or more hours before breakfast. This is inconvenient and in our experience has rarely been satisfactory.

(*b*) The dietary carbohydrate may be redistributed, one-fifth of the day's allowance being given for breakfast, two-fifths for lunch and two-fifths for supper. Indeed, it has been our recent practice to arrange the diet in this manner on the first day of treatment rather than waiting until the necessity for the change becomes apparent. Such a distribution imposes less of a burden on the slowly acting insulin soon after it is injected, reserving the greater demands for a time when its hypoglycemic effect is well under way, and constitutes a logical basis for the further adjustment of food and insulin which is often necessary.

With the diet apportioned as above and with a given dose of protamine insulin, the patient may react in one of several ways:

1. Control of the blood sugar may be good throughout the 24 hours.

2. The fasting blood sugar may be normal but hyperglycemia still occur after some of the meals. In this event the dose of protamine should not be altered, but a further redivision of carbohydrate must be made. We have been surprised at what small changes sometimes accomplish the desired result.

* This patient required two daily injections of protamine-calcium-insulin. It has not been possible to rehospitalize her for trial with the material containing added zinc.

In the case of R. B. (figure 1, July 22, 23), for example, the subtraction of only 5 grams of carbohydrate from breakfast and its addition to supper spelled the difference between poor and good control. Since the fasting blood sugars on July 21 and 22 were already normal, the slight increase in the dose of protamine on the

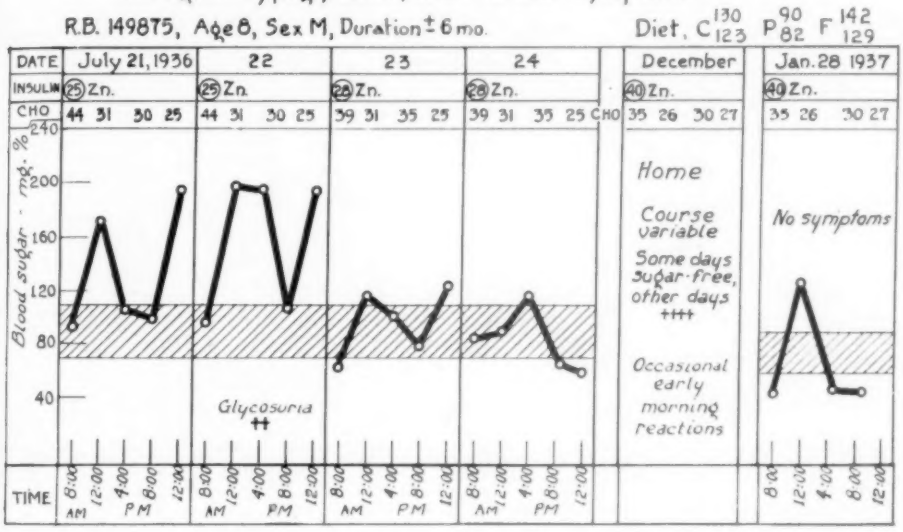

FIG. 1. Protamine-zinc-insulin is indicated by figures within circles followed by "Zn." Regular insulin in succeeding charts is shown by figures without circles. The third line shows the distribution of dietary carbohydrate (not total glucose value) between breakfast, lunch, supper and bed time. The shaded area represents the average normal range of blood sugar for the method used. In this case post-prandial hyperglycemia was well controlled by small changes in carbohydrate distribution and dosage of protamine insulin. The dose, however, need not have been increased since the blood sugar during fasting was already normal. Note symptomless hypoglycemia on Jan. 28, when the blood sugars were obtained in the out-patient department.

twenty-third and twenty-fourth was probably superfluous and, indeed, led to mild hypoglycemia.

The case of A. F. (figure 2) is similar. The division of carbohydrate in the proportion of 20–40–40 on June 6 resulted in hypoglycemia before lunch. On June 8 the ratio of 30–40–30 was unsatisfactory. The mean of 25–40–35 reached on June 10, however, gave adequate control throughout the day.

In principle, obviously, carbohydrate should be deducted from the meal following which hyperglycemia occurs, and added to the meal following which the blood sugar is low. Our experience with patients who are sensitive to such small shifts in carbohydrate is at variance with that of other writers [9, 12, 13, 18], who imply that with protamine insulin considerable latitude in diet is permissible.

3. The fasting blood sugar may be too low, with or without glycosuria

during the day. In this case, either (1) the dose of protamine must be reduced until the morning blood sugar is normal, any resulting daytime hyperglycemia being cared for by dietary adjustment, or (2) the dose of protamine may be kept the same and a bed-time feeding of 10 to 30 grams of carbohydrate given. If glycosuria occurs after meals, the bed-time carbo-

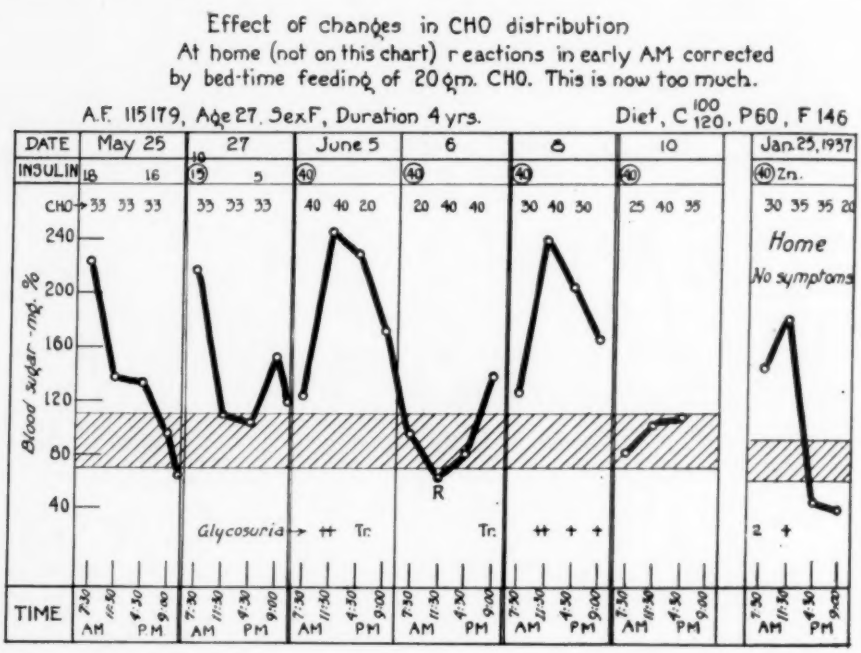

FIG. 2. Though well controlled when discharged from the hospital (June 10), increased activity at home led to early morning hypoglycemia which necessitated a bed time meal. The distribution of carbohydrate (30–35–35–20) which gave an unsatisfactory curve on Jan. 25 has now been changed to 25–40–40–15 with good results. The letter R in this chart and succeeding ones indicates insulin reaction. Note symptomless hypoglycemia on Jan. 25.

hydrate should be obtained by deducting small amounts from the meals at the times indicated rather than by adding it to the total daily allowance; the latter procedure is apt to result in an increase in the total insulin requirement. If, on the other hand, post-prandial hyperglycemia does not occur on the given dose, the carbohydrate taken on retiring may be added to the total daily allotment with only slight, if any, change in the dose of protamine. About two-thirds of the patients in this series have required a bed-time meal.

The case of H. G. (figure 3) illustrates some of these points. The total diet of carbohydrate 150 grams, protein 75 grams and fat 120 grams was maintained throughout. On Jan. 19, with the carbohydrate distributed 50–50–50, 35 units of protamine insulin, following the 10 units of regular insulin given the evening before, proved to be too much. The dose was accordingly dropped to 25 units, and since the highest blood sugar on the nineteenth had occurred before lunch, the carbohydrate

was divided 30–60–60. It is apparent from the blood sugar curve of January 21 that now the breakfast was too small and the lunch and supper were too large. Therefore the diet was rearranged by adding 10 grams of carbohydrate to breakfast and subtracting 20 grams from lunch and 10 grams from supper, the extra 20 grams thus

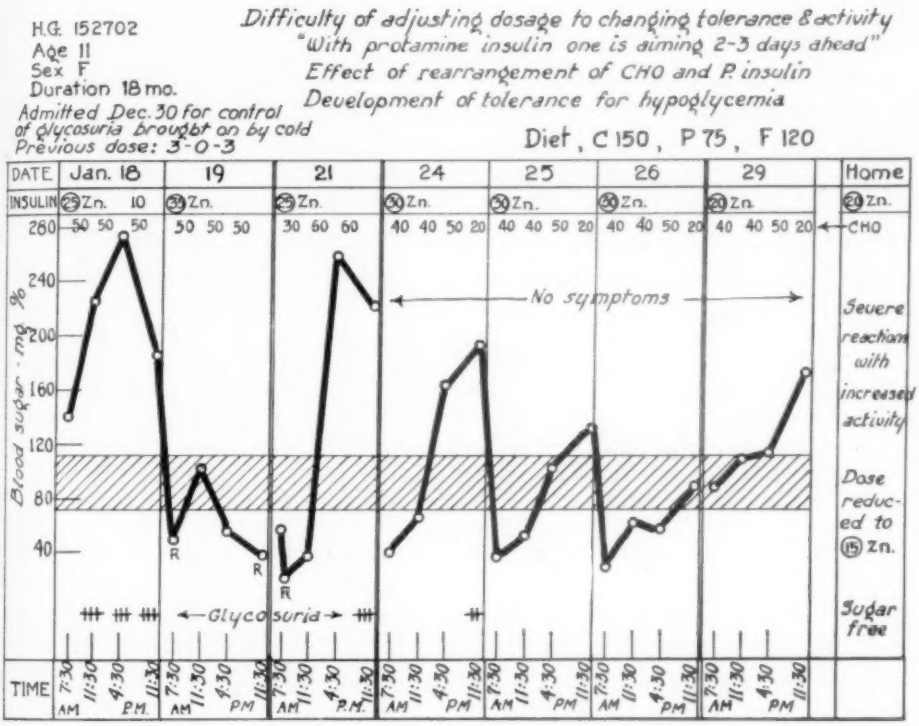

FIG. 3. This patient was transferred to protamine insulin at the time when her tolerance for carbohydrate was improving after recovery from a cold. This procedure under such circumstances is often attended by difficulty. It was a mistake to attempt to control afternoon and evening hyperglycemia by raising the dose of protamine insulin on Jan. 19 and 24 because the dose of the preceding day in each case had already produced hypoglycemia before breakfast. Note progressive improvement in blood sugar curves from Jan. 24 to 26 despite no change in carbohydrate distribution or dosage. For further discussion see text.

obtained being given at bed-time. The resulting proportion of 40–40–50–20 was found satisfactory except for the persistence of early morning hypoglycemia. This was due to the erroneous increase in the dose of protamine from 25 to 30 units between January 21 and 24 in a mistaken effort so to control the day-time hyperglycemia exhibited on the former date. When the dose was reduced to 20 units hypoglycemia was eliminated (January 29).

It may be stated here that the distribution of protein and fat between the various meals is unimportant. Also, in common with Campbell [3] we have found the lower carbohydrate diets more satisfactory than those of higher value.

4. The blood sugar throughout the day, including that before breakfast, may be maintained on too high a level. In this relatively happy circumstance the dose of protamine insulin must clearly be increased.

5. Only rarely have we observed hyperglycemia before breakfast with hypoglycemia later in the day. In the case of A.F. (figure 2) the curve obtained on January 24 led to a subsequent change in carbohydrate distribution from 30–35–35–20 to 25–40–40–15, the dose of protamine insulin being left the same.

6. In certain cases, with an amount of protamine insulin which gives a normal blood sugar before breakfast, glycosuria during the remainder of the day may be poorly controlled despite every effort properly to readjust the dietary carbohydrate. This situation usually requires a small dose (5 to 15 units) of regular insulin given at the same time as the protamine. In our experience with this group of patients to date, the administration of supplementary unmodified insulin before breakfast, provided carbohydrate was properly distributed, has been sufficient to take care of hyperglycemia in the afternoon as well as that occurring before lunch.

The case of J. L., a severe diabetic, is illustrative (figure 4). The blood sugar curve obtained on January 21 in the out-patient department shows that a dose of protamine insulin (50 units) sufficient to give reasonable control through the day,

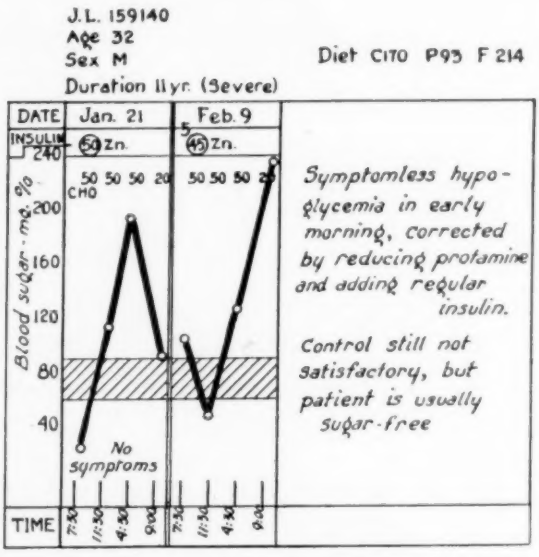

FIG. 4. Effect of a small dose of supplementary regular insulin substituted for an equal amount of protamine insulin.

produced marked hypoglycemia in the early morning. Reduction of the dose to 45 units corrected the hypoglycemia but resulted in heavy glycosuria after meals. The curve of February 9, with 45 units of protamine and 5 units of regular insulin, is more, though not completely, satisfactory.

The case of T. L., also a severe diabetic (figure 5) is similar. Here 7 units of regular insulin were added to the amount of protamine. This, while producing hypoglycemia before lunch, permitted hyperglycemia in the afternoon. The amounts of

protamine and regular insulin, therefore, were continued unchanged, and adequate control was established by changing the proportion of carbohydrate from 25–55–35–20 to 35–45–35–20.

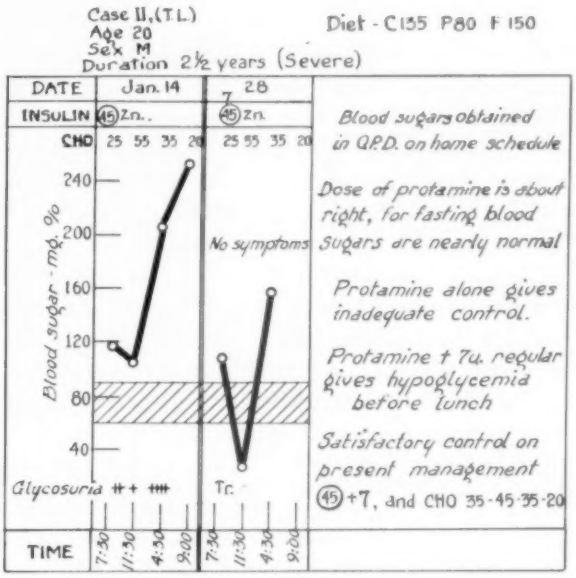

FIG. 5. Effect of supplementary regular insulin added to the amount of protamine insulin.

(*c*) Since protamine-zinc-insulin has been available it has not been necessary in any case of this series to use the method originally described by Hagedorn of giving regular insulin in the morning and the slowly acting insulin at night.

ASYMPTOMATIC HYPOGLYCEMIA

It has been noted by nearly all workers that, probably due to the slowness with which the blood sugar falls, the hypoglycemia caused by protamine insulin is insidious in onset, symptoms may be slight and the level of blood sugar at which symptoms do occur is lower than when regular insulin is used. These facts find confirmation in the cases here reported (figures 1, 2, 3, 4, 5, 6). They may account in part for the common observation that reactions are fewer with protamine than with regular insulin, though it must be admitted that reactions are less frequent also because the blood sugar is better controlled.

We would especially call attention to that group of patients who, though discharged from the hospital well controlled, were found to have abnormally low blood sugars with no subjective manifestations when they were recalled to the out-patient department for analyses of the blood made under what roughly approximated home or routine conditions (figures 1, 2, 4, 5). It should be pointed out that the method for blood sugar * used in the out-

* Analyses are done on unlaked blood filtrates [5] by the Somogyi modification [17] of the Shaffer-Hartmann method.[16]

patient department gives values for normal (60 to 90 milligrams per 100 c.c.) which are somewhat below those obtained by the customary Folin-Wu procedure. Nevertheless, the levels at which some of these blood sugars were found are disconcertingly low. The patient J. L. (figure 4), for example, walked into the clinic one morning feeling perfectly well with a blood sugar of 26 milligrams per 100 c.c. While the effect of prolonged, subclinical hypoglycemia in the human is not known with certainty, there exists the distinct possibility that functional derangement or even structural damage to tissues may result.[19] Wilder states that he is informed of one death following the use of protamine insulin. When a patient is discharged from the hospital using regular insulin, the increased tolerance for carbohydrate incident to resumption of normal activity causes but little concern with regard to the possible development of hypoglycemia, for the appearance of symptoms is a reliable guide to dosage. With protamine insulin, however, the patient is often deprived of a valuable warning signal, and the only indication of danger may be a laboratory report. It is therefore important that patients who have been sent home taking protamine insulin be requested to return to the office or clinic on two or three occasions when the urine is known to be sugar free for analysis of the blood for dextrose. Since hypoglycemia is most apt to occur in the early morning, this precaution is especially to be observed when the urine specimen passed on arising does not reduce copper.

Others [18, 19] have directed attention to the difference in symptomatology between reactions due to regular insulin and those due to the protamine compound. Wilder has pointed out that in the case of the latter, the relative lack of perspiration, tremor and palpitation, and the common presence of headache, drowsiness, weakness and sometimes nausea and vomiting may give the impression of acidosis rather than hypoglycemia. The patient must be warned of these differences and instructed to test the urine when in doubt. Paresthesia is a common manifestation. Another peculiarity is that patients who are in unrecognized hypoglycemia may suddenly be precipitated into unconsciousness by a little unusual exertion. The tendency of symptoms to recur after being relieved by carbohydrate has been remarked by a number of observers.[3, 9, 13, 14, 18]

Difficulties Due to Delay in Appearance of Full Effect

Sprague and his colleagues [18] have said of the unmodified protamine insulin, "When using insulin-P, one is aiming about 72 hours ahead." This axiom is even more applicable to protamine-zinc-insulin and is well illustrated by the case of H. G. (figure 3, Jan. 24, 25, 26), in which the blood sugar curve showed progressive improvement over three successive days with no change in the amount of insulin or distribution of carbohydrate, though it was maintained, to be sure, on too low a level. The logical deduction is that changes in dosage should not be too frequent or pronounced

For the physician schooled in the use of ordinary insulin this is not an easy lesson to learn. The temptation to increase the dose of protamine insulin daily when the patient is excreting sugar is difficult to resist. The lapse of 48 or 72 hours, however, may show that an alteration contemplated earlier would have been not only unnecessary but confusing. It is our belief that many unsatisfactory results, including some of our own, are due to failure to recognize this truth.

The slow and prolonged action of protamine insulin has several disadvantages.

(*a*) It lengthens the period of stabilization in severe cases. This means additional expense. We have rarely found it possible to reach a satisfactory adjustment with hospitalized patients short of 10 to 14 days, and with outpatients a longer time, with frequent visits, is required.

(*b*) It renders difficult the transfer to protamine insulin of patients whose tolerance for carbohydrate is rapidly improving, such as those recovering from acidosis, infections and surgical operations.

The patient C. G. (figure 6) for example, had been brought out of acidosis and maintained with regular insulin for 10 days after his admission in pre-coma. About the eleventh day (January 8) his tolerance began to improve and the dose of 90 units of regular insulin proved excessive. On January 9, when treatment with protamine insulin was begun, the total dose was accordingly reduced to 80 units (70 of protamine and 10 of regular insulin). This, while apparently satisfactory for the day in question, led to reactions the next, and for the following three days, despite daily reductions in dosage, the patient was in severe, almost constant hypoglycemia due to our inability to estimate the speed at which his insulin requirement was decreasing. Finally no insulin of any kind was given after the injection of 35 units of protamine on the morning of January 12, and not until January 14 did the blood sugar rise appreciably above the normal. On January 15 treatment was resumed with smaller amounts of protamine insulin.

It is probable that in this case the exclusive use of regular insulin, with its relatively short latent period and duration of action, until complete stabilization had been reached would have yielded better results than those obtained by the more prolonged and inflexible action of protamine. On the basis of similar cases we are now reluctant to transfer a patient to the new insulin until a definite plateau of tolerance has been attained with ordinary insulin. Again, it is important to recognize that, with patients who require more than 20 or 30 units daily, this means either extended hospital care over a single period of time or rehospitalization for the express purpose of making the transfer after tolerance has become established under management at home.

Joslin [7] has stated that the regulation of a previously untreated diabetic with protamine insulin is a much simpler matter. Our experience with this procedure has been limited but encouraging.

(*c*) Protamine insulin theoretically is disadvantageous in diabetic emergencies such as coma, infection, childbirth and operations. In all these the

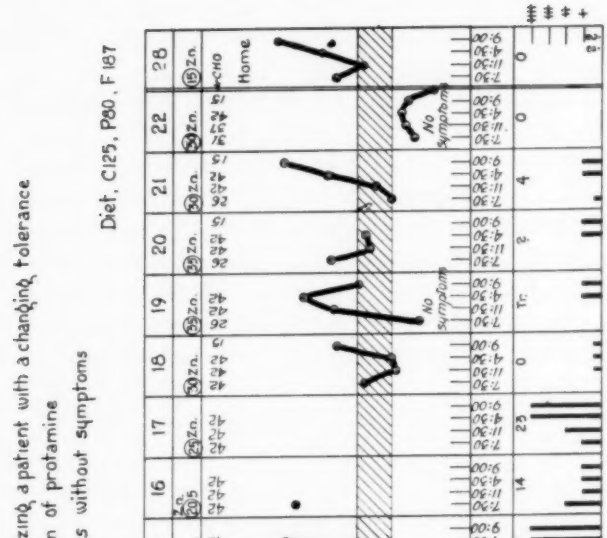

FIG. 6. For discussion see text, p. 787.

condition of the patient is subject to rapid fluctuations against which a quickly acting, easily variable insulin would seem to be the weapon of choice. Exceptions to this view would be emergencies arising in patients already under treatment with protamine insulin. In such cases, as suggested by Colwell [4] and implied in the report of Kepler, Ingham and Crisler,[10] it may be wise to continue the basic dose of protamine insulin, supplementing it by regular insulin. The employment of the two kinds of insulin in cases of acidosis in which the protamine compound has not previously been used has been reported favorably in a few instances,[10, 19] but the question of whether this unnecessarily complicates treatment cannot be answered finally without further experience.

(*d*) The prolonged effect of protamine insulin may, under certain circumstances, involve difficulty of yet another sort. If once a day's supply has been injected under the skin, a sudden illness should prevent the taking or retaining of food, serious hypoglycemia would be likely to ensue unless dextrose were administered parenterally at intervals for 24 hours or longer. One case of this kind has been brought to our attention.

Allergy

Three patients in this series developed red, raised, itching lesions at the sites of injection a few days after starting treatment with protamine insulin. One of these had taken ordinary insulin irregularly at home without urticarial reactions. The other two had never received insulin of any sort. In each case the local allergy disappeared spontaneously within a week or two despite continuance of the injections. Joslin [9] mentions two similar cases not observed by him.

General Principles Governing the Use of Protamine Insulin

Although the treatment of patients with protamine insulin is a highly individual matter, the combined experience of a number of investigators permits the establishment of certain general principles which at least for the present should govern its use. These can best be discussed as applying to two classes of patients.

I. *Patients Who Should Begin the Use of Protamine Insulin Only in the Hospital.* This class includes all children, and those adults whose disease is severe or complicated, who are unstable and who live so far from a laboratory that determinations of the blood sugar are not feasible. These patients fall into two groups:

(*a*) Those who have not received insulin of any sort. Such patients may be treated either by (1) starting the administration of protamine insulin at once, with or without supplementary doses of regular insulin, or by (2) stabilizing the patient entirely with regular insulin and then transferring to protamine insulin.

Although in a few cases reported by other writers [10, 13] coma has been treated with protamine insulin alone, it would seem safer for the time being to manage all previously untreated cases with severe acidosis, infection or surgical complications by means of regular insulin only. The transfer to protamine insulin should be made as outlined in (*b*) below and only after a definite plateau of tolerance has been reached.

The other patients in this group may be given protamine insulin uninterruptedly from the time of admission. The dietary carbohydrate should as a rule be apportioned ⅕ for breakfast, ⅖ for lunch and ⅖ for supper. A single injection of protamine insulin, the amount determined by an "educated guess," is given each morning an hour before breakfast, supplemented if necessary by a smaller dose of regular insulin at the same time. Although some authors [3] have found it permissible to give the two kinds of insulin simultaneously in the same syringe, the majority agree that this procedure leads to the precipitation of a certain and probably variable portion of the regular insulin by the protamine present and tends to yield inconstant results. The same syringe may be used provided that the regular insulin be withdrawn and injected first, but the sites of injection should be separate. Specimens of the urine and, if possible, the blood, are obtained on arising and three hours after each meal and examined for sugar. Unless grossly inadequate the dose of protamine insulin should not be changed before three or four days or more have elapsed. As improvement occurs the regular insulin may be reduced and finally omitted, although in some cases its permanent use is necessary. Further rearrangement of carbohydrate should be made as indicated. The safest and best guide to the proper amount of protamine insulin is the level of the blood sugar in the early morning. In order to allow for the effect of increased activity at home, it is a wise precaution to discharge hospital patients with a dose which permits slight hyperglycemia.

(*b*) Those who are already receiving regular insulin. In these cases it is usually best to begin with an amount of protamine equal to the total daily requirement of regular insulin. For the first few days, at least, glycosuria is better controlled by giving simultaneously but in a different site a dose of regular insulin equal to from one-third to one-fourth of this amount. The regular insulin may be in addition to the protamine used, or may be substituted for an equal quantity of the latter, depending on the case. In most instances it is possible to decrease the dose of regular insulin a few units at a time over a period of three or four days until finally protamine insulin alone is given.

II. *Patients Who Can Safely Begin the Use of Protamine Insulin in the Office or Out-Patient Department.* These patients are adults whose disease is uncomplicated and of only moderate severity, who give promise of being fairly stable and who live within convenient distance from a laboratory. They also fall into two groups:

(*a*) Those who have not received insulin of any sort. Joslin [7, 8] emphasizes the safety, simplicity and wide applicability of using only protamine insulin in such cases. A patient of this type, *provided he shows no ketosis,* should be given a diet, weighed if possible, with the carbohydrate divided ⅕ for breakfast, ⅖ for lunch and ⅖ for supper, and should be taught the technic of urinalysis, tests being made on arising and about three hours after each meal. Having been instructed in the method of administration, he should be told to take one hour before breakfast a dose about one-third less than that which, on the basis of experience, the physician thinks may be his requirement. This dose should not be changed for the next three or four days, the patient meanwhile testing the urine as described and communicating the results to his doctor daily. It is far better to start with a relatively small dose of protamine insulin and permit glycosuria for a few days than to begin with too large a dose which may, in 48 or 72 hours, produce hypoglycemia in the early morning. The dose can be increased more easily than it can be reduced. Subsequent changes in dosage should not be made daily. When the urine tends to become sugar free, and particularly if the specimen on arising is clear, a determination of the fasting blood sugar should be made, or if this is impossible the dose should be reduced a few units every three or four days until sugar reappears in the urine, then raised a notch. If hypoglycemia does develop, the dose should be promptly dropped to a level calculated to result in glycosuria and again be built up gradually. By this time further adjustments in carbohydrate distribution as described earlier may be necessary, including possibly a bed-time feeding. If any unusual difficulties are encountered the patient should be hospitalized.

(*b*) Those who are already receiving small or moderate amounts of regular insulin. It is our belief that in this group only the patients who are comparatively stable and who require not more than 20 or at the most 30 units daily should be transferred to protamine insulin outside the hospital.* Since the supervision of ambulatory patients cannot be so close as that of hospital patients, the initial dose of protamine insulin should be equal to only about two-thirds of the previous total daily requirement, the other third, more or less, being given as regular insulin. The next day half the amount of regular insulin, or possibly none at all, depending on the urine tests, may be given. Further adjustment of diet and insulin may be made as outlined in the preceding paragraphs.

Because the hypoglycemia produced by protamine insulin is so commonly asymptomatic, the importance of making frequent determinations of the blood sugar, both during the period of adjustment and after the patient has gone home, cannot be overemphasized.

* Richardson and Bowie [14] using unmodified protamine insulin, have reported the outpatient transfer of over 30 patients whose requirements were less than 40 units daily.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

SOME OF THE PRACTICAL PROBLEMS IN THE SERUM THERAPY OF BACTERIAL INFECTIONS *

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SERUM therapy is an outgrowth of the discovery that microörganisms, the bacteria, are incitants of infectious disease. As such, it is difficult to differentiate the results of the branch from those of the parent stem. For example, in diphtheria, early diagnosis with prompt isolation has alone had a far-reaching effect not only upon the morbidity but also, indirectly, upon the severity of the disease; and it is difficult to distinguish the effect of the discovery of the diphtheria bacillus and of improved public health methods from that of the specific treatment with antitoxin, on the morbidity and mortality of the disease. Much of the decline is to be attributed to advancing medical science, apart from specific serum therapy, as exemplified in the diminishing morbidity and mortality of other infectious diseases. Much of the lowered mortality of diphtheria, however, may be accredited to treatment with antitoxin, and these results have reached an astounding magnitude when measured in terms of human happiness and welfare.

Forty years' experience with diphtheria antitoxin illustrates very strikingly the major problems of serum therapy. In some respects they may vary according to the disease and its bacterial incitant; in others, they do not differ materially. These problems may be classified under two main headings: one, the preparation of potent, effective sera in the laboratory; the other, early treatment with adequate dosage at the bedside. Preparation of diphtheria antitoxin has advanced steadily. There has been marked improvement as evidenced by a more than tenfold reduction in dosage and an even greater increase in potency. No one now criticizes the quality or questions the potency of the diphtheria antitoxins that are distributed under governmental supervision and control. Corresponding reduction in mortality at first paralleled the improvement in antitoxin, but there is now a residual mortality that eludes even this specific therapy. The residual mortality in diphtheria is now to be attributed to delayed treatment or inadequate dosage, possibly entirely to delayed treatment. It would be important from a public health standpoint to have complete information regarding every fatal case of diphtheria.

Effective serum therapy depends primarily upon the neutralization of toxic substances; secondarily, upon the destruction of the bacterial incitant.

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The extent to which one process is dependent upon the other, as well as the precise sequence of events in the different infectious diseases, offers a most important field for investigation. Unfolding knowledge of group and type specificity reveals the subtle interrelationships of the antitoxic and antibacterial activities of serum in relation to the protective mechanism of the tissues of the host that underlie effective serum therapy.

The antitoxic action of serum therapy has been contrasted very sharply with the antibacterial phenomena attributed to the sera that are used in the specific treatment of infectious diseases, the bacterial incitants of which invade the tissues generally. So sharply have these two activities been differentiated that the antitoxic action of the antibacterial sera has been overshadowed. In the laboratory, studying the different activities or manifestations of immune sera, it is important to classify and differentiate sharply, but when one turns to the study of effective serum therapy in the infectious processes of the tissues, it is not only difficult but unwise to differentiate these activities.

Sera differ in their antitoxic and in their antibacterial action, but just how they differ and to what extent, or how they are interdependent and to what extent, is of paramount concern to us all since these relationships underlie all phases of vaccine and serum therapy. The type specificity of botulinus antitoxin on the one hand, and on the other, the type specificity of the antipneumococcus sera represent extremes.

Antitoxic serum exerts an antibacterial effect, possibly directly, but more obviously indirectly upon the incitant of infection in the tissues. The diphtheria, tetanus, and botulinus antitoxins are the most representative. With diphtheria and tetanus infections, group and type specificity are not involved, despite the fact that strains of these microörganisms vary widely in their toxigenicity and antigenicity; not that the diphtheria bacillus may not be divided into subgroups on the basis of selected characters, but that the toxin produced by the different strains has invariably been neutralized by the standard antitoxin. In diphtheria, the administration of antitoxin neutralizes the toxin and crisis occurs promptly. Following this, the diphtheria bacilli are destroyed by the protective mechanism of the tissues unless these bacilli are so situated that they evade the action of the tissues and survive as relatively harmless parasites in the carrier state. However, when the disease has progressed to a later stage, the tissues are vitally injured. Neutralization of the free toxin by antitoxin is inadequate and the protective mechanism fails to destroy the diphtheria bacilli. These examples of the simplest form of serum therapy very strikingly illustrate its fundamental limitations. Tetanus antitoxin acts similarly. The tetanus bacillus, however, is less readily established as a parasite in the tissues when its toxic activity ceases to injure the tissues. Recovery, when it occurs, is complete in that the incitant does not persist as a parasite in the tissues. Although group or type specificity does not figure in serum therapy of tetanus or diphtheria infections, the toxigenicity and antigenicity of different strains

of these microörganisms are most important factors in the production of potent antitoxins.

With the incitants of botulism, which is also a simple toxemia without invasion of the tissues by the incitant, type specificity plays an important rôle in serum therapy because the neutralization of the toxins in the test tube as well as in the tissues depends upon the homologous relation between the incitant and the antitoxin that is used in serum therapy. Thus, the antitoxin of A, of B, and of C microörganisms is effective only in the corresponding infections of A, of B, and of C types. The limitations of serum therapy, as illustrated by the above cited examples of diphtheria infection, are even more sharply defined in botulism. To be effective, an antitoxin must be administered almost immediately. The crisis of the disease process, irrespective of serum therapy, occurs promptly because the disease is so largely a toxemia and practically uncomplicated by even a localized infectious process. In fact, the majority of the cases are simply the absorption of a large amount of toxin. The crisis occurs so promptly that the patient either dies or recovers irrespective of the administration of serum. Nevertheless, the antitoxin should be given because, after all, it is impossible to determine by any clinical signs whether the crisis has been reached or passed.

An antitoxic serum exerts an antibacterial effect when it is used in the treatment of an infectious process the incitant of which is localized, and the disease largely, if not entirely, toxemic in character. Moreover, antibacterial sera exert an antitoxic effect either directly or indirectly upon the incitant of the more generalized infectious diseases. The antipneumococcus and antimeningococcus sera are representative examples of antibacterial sera. Antipneumococcus serum exerts definitely specific action, sharply defined according to the type specificity which is related to the carbohydrates of the microörganisms. The direct antibacterial action is well recognized and is evident in the protection test in mice and the effect of the serum on phagocytosis.

In the absence of demonstrable toxin, it is difficult to obtain evidence of an indirect antibacterial action associated with an antitoxic activity that conserves the tissues and favors the destruction of the pneumococci by the protective mechanism that follows neutralization of the toxin. However, the antitoxic action is manifested by the critical effect of the serum on the febrile reaction of pneumonia corresponding to the crisis that occurs spontaneously. The neutralization of the toxin may precede or follow the destruction or inhibition of the pneumococci in the tissues. However, following neutralization of its toxic activity, the pneumococcus may persist as a parasite relatively harmless to its host, as evidenced by survival of the pneumococcus after the crisis of pneumonia, and in the highly immunized animal when it becomes attenuated and its toxic activity nil. The virulence of these pneumococci is lost; they are no longer toxic but continue as parasites.[1] Thus it is that the antibacterial antipneumococcus serum doubtless

exerts an antitoxic as well as an antibacterial effect when it is used in the treatment of pneumonia.

The antimeningococcus serum also, quite similarly, exerts a definite and specific effect. The antitoxic activity of this serum is, at present, stressed. As in pneumonia, there has always been clinical evidence that the serum exerted a marked antitoxic as well as antibacterial effect. On account of the general insusceptibility of laboratory animals to infection, it has been and is difficult to differentiate the antitoxic and antibacterial action of antimeningococcus serum. However, results of protection tests in mice [2-5] with cultures suspended in mucin do distinguish different degrees of activity in different sera. The intracutaneous test [6] and protection tests against lethal doses of toxic extracts or filtrates in animals [7-13] are not yet of practical value in the titration of antitoxic potency.

Antistreptococcus sera exert definite and specific antitoxic and antibacterial effects in the treatment of infection. The specific relationship is marked and complicated with the streptococci because it relates not only to the antitoxic activities of the serum and the antigenic activity of the toxins in producing the antitoxic serum,[14, 15] but also to the antibacterial activity of the serum as it is manifest in the protection test.[16-19] The study of antistreptococcus serum, even in its present elementary stage, has revealed the most striking and convincing demonstration of how essential are the antitoxic, as well as the antibacterial activities of the serum to an effective serum therapy of streptococcus infection as soon as it has become generalized. In the earliest stages of certain infections, the antitoxic activities [20, 21] may suffice as they do in diphtheria. The direct antitoxic effect in neutralizing the toxin and the indirect antibacterial effect by favoring the protective mechanism of the tissues suffice to determine recovery—possibly with or even without any direct antibacterial action of the serum. In all these actions and reactions, however, the homologous relations are important on account of the marked type and toxin specificity manifested by the different hemolytic streptococci.

Although specificity of the toxins is well marked, it has no relation to the disease processes incited by the hemolytic streptococci—scarlet fever, erysipelas, puerperal fever, etc. No specific etiological relationship has as yet been established. The toxic activities of the different strains vary greatly not only in potency but in character. Similarly, the antigenic potency and valency also vary with the strain and irrespective of the toxin group, specificity, or titer of the toxins.

The antitoxic activities of the serum thus accordingly vary.[15, 22-26] Within a group the potency of serum produced with one strain may be high and the valency narrow, whereas in that produced with another strain, the converse may obtain. Although in general the neutralization of the toxin takes place in the homologous relation according to groups, the potencies and valencies of the different antitoxic sera vary widely. Combination of representative sera may broaden the valency beyond that manifested by either

serum separately. As a result of the study of more than 1500 cultures, two strains have been selected with which, in combination, it has been possible to obtain an antitoxic serum of such broad valency that the toxins of all strains encountered thus far are neutralized. Finally, and what is of the utmost importance, qualities may be supplied by the tissues of the animal host, which doubtless account in large measure for the manifestations of the antitoxic as well as the antibacterial effect of heterologous sera in infectious processes whether studied clinically in the treatment of human infection or experimentally in animals.

Factors which further complicate the problem of effective serum therapy with all of these bacteria are differences in the cellular susceptibilities of the microörganisms themselves as well as the activities of the tissues in their presence. For example, the biologic stability and also, so to speak, the fragility of the pneumococcus cell in disease processes, together with its capacity for adaptation, are determining factors in the serum therapy of pneumonia as they are in the prognosis of the untreated disease.

The thermal limits of growth, depending upon the strain and a favorable environment, vary with the pneumococci from 39° C. to about 41° C.[27, 28] In immune serum, the pneumococcus cell vegetates at 37° C. At temperatures above the thermal limits of growth, varying degrees of lysis may take place. Hyperthermy, experimental elevation of body temperature, may inhibit, or even eliminate temporarily, the pneumococcemia of some infections in susceptible animals, whereas it may hasten the course of others.[29] Treatment with immune serum induces crisis in the febrile reactions; there is neutralization of the toxemia and marked destruction of the bacteria. The pneumococcus cell is fragile, and especially so if compared with the streptococcus, although the thermal limits of growth of many strains of hemolytic streptococci do not exceed materially those of some of the pneumococci.[27] Immune serum in streptococcus infection may induce pseudo crises in the febrile reaction without affecting to a corresponding degree the bacteremia which may, and often does, progress. The streptococci, moreover, produce a toxin, and, like strains of the diphtheria bacillus, vary greatly in this respect. Certainly the quantities produced by some of the streptococcus strains can scarcely be recognized experimentally; yet when these streptococci invade the tissues of a host, the febrile reaction induced is convincing proof of their toxigenic capacity. The toxin of the pneumococcus, when this microörganism is cultivated in vitro, has not been recognized; yet the febrile reaction of pneumonia is convincing proof of the toxigenic activity of this incitant of infection. The pneumococcus is toxigenic when developing in an animal host but not under ordinary experimental conditions in vitro. Effective antibacterial sera in the treatment of pneumococcus and meningococcus infections are produced by the immunization of horses with living virulent cultures. Moreover, antitoxic streptococcus sera of the highest potency, in my experience, can only be obtained with living cultures and as a

result of the development of the streptococci in the horses undergoing immunization.

Evidence of wide variation in the subtle cellular susceptibilities of the bacterial incitants of infection accumulates when the toxigenic and antigenic activities are studied for the purpose of preparing therapeutic sera of high potency and broad valency. The criteria for the selection of cultures for antitoxin are sharply defined: a potent toxin of high antigenic value must be produced. The vicissitudes of maintaining, not to mention developing, diphtheria strains for antitoxin production during the past 40 years are well known. Even more convincing is recent experience with the selection of strains of the hemolytic streptococci for the preparation of therapeutic serum. The same criteria in use for the diphtheria cultures must be fulfilled, and, in addition, there must be taken into account qualitative as well as quantitative differences in the kind of toxin produced in relation to its antigenic activity.

The criteria for the selection of cultures for production of the so-called antibacterial sera are not so sharply defined, apart from the empirical test of producing potent therapeutic serum. For the pneumococci, virulence and possibly carbohydrate production are practically the only guides. For the meningococcus, until very recently, the agglutination reaction has been one of the most valuable aids because the valence and antigenicity can be determined within the limitations of the significance of this reaction.[30-32] The precipitation reaction,[33-35] the virulence test with mucin in mice,[2] and several tests of toxic activity [6, 8, 36-38] are now available to demonstrate comparative differences in strains. It still remains, however, to correlate these various activities of the culture with its efficacy in the production of potent therapeutic sera. The selection of freshly isolated strains has been stressed, but these strains vary, and it is perhaps far more important to select stable representative strains of proved high antigenic potency and broad antigenic valency and, as is now practicable, to maintain their biologic status.[2, 3, 31, 32, 34, 39-41]

An immediate practical problem concerns the value of concentration or separation of the active globulins of antitoxic and antibacterial sera. In addition to economic considerations, there is the question as to whether or not the loss which concentration entails is due entirely to the failure to recover all of the active substances or whether certain supplementary or complementary activities of the sera are eliminated. Certainly it is not conceivable that there is a gain in therapeutic value save as the result of elimination of extraneous protein which may have a deleterious action as evidenced by the greater proportion of serum reactions with the unconcentrated serum as compared with the concentrated. However this may be, the concentration of diphtheria antitoxin, for example, has become an established procedure. Moreover, physicians at the bedside will invariably administer refined preparations in preference to the untreated serum. Concentration as it relates to the preparation of the antipneumococcus, anti-

meningococcus, and antistreptococcus sera, has only recently been adopted. It has, however, become essential from a practical point of view. Experience with the concentrated as compared with the unconcentrated products is limited to a comparatively short period. Moreover, during the past decade there has been a marked improvement, as a result of experience in their preparation, in the therapeutic value of all of these sera generally available. The potency has been materially advanced and the valency broadened. The data and statistics are, therefore, not generally comparable —quite apart from the variations in the severity of the infections treated with the different sera. I therefore do not feel competent to evaluate the reports of other observers and have been forced to rely upon personal experience with the sera prepared in our laboratory during this period. Fortunately some direct comparisons are possible from the data that have been collected through the kindness of Dr. Cole of the Rockefeller Hospital and of Professor Longcope and Professor Park of Johns Hopkins Hospital, who have had opportunities of comparing the unconcentrated and the concentrated sera prepared by identical methods and of equivalent potencies and valencies. These data I consider reliable.

During the short period that the sera have been refined by special methods,[42-44] 25 cases of type-I pneumonia have been reported by Dr. Abernethy from the Rockefeller Hospital[45]; three more may now be added to this series in which no fatalities have occurred. In an earlier series of 371 cases treated with unconcentrated serum, Cole reported a mortality of 10.5 per cent.[46] The results in these two series, however, are not strictly comparable. In those cases treated with the concentrated serum the Neufeld technic was available. The prompt type diagnosis thus provided accounts for an earlier administration of serum, and under these improved conditions of treatment a lower mortality may well follow. In 89 cases of meningococcus meningitis treated at Johns Hopkins Hospital with the concentrated product alone, there were 8 deaths (8.9 per cent). In 31 cases which were given both concentrated and unconcentrated serum, there were 3 fatalities (9.7 per cent). During the same period, 32 patients were treated with the unconcentrated serum with 4 deaths (12.5 per cent). In each group the fatal cases included some which had complications of pneumonia or which were moribund when admitted, but survived the first treatment longer than twenty-four hours. Dr. Tillett reported on a group from this series in 1935.[47] These results cannot be credited wholly to the serum that was used because they may be due quite as much, or even entirely, to early treatment with adequate dosage. Serum reactions were materially diminished with the concentrated preparations. Some reactions, however, have been noted with the concentrated antimeningococcus serum when given intraspinously, although the percentage of protein does not materially exceed that of the untreated serum.

Problems of serum therapy thus relate to the preparation of the serum on the one hand and, on the other, to its administration. The selection of

strains according to their toxigenicity, antigenicity, and valency is of first importance in the preparation of the antibacterial serum as it is with the antitoxic sera, and especially is this true when type specificity is involved. The quality and potency of the diphtheria antitoxins are now no longer questioned. There has been steady improvement in the antibacterial sera during the past ten years. It has been possible to select representative strains of the meningococci, the antigenic potency and valency of which make it possible to prepare effective polyvalent antimeningococcus serum. The antigenic properties of these strains can be maintained in the laboratory so that it is unnecessary to resort to freshly isolated strains, save as a means of replenishing or improving standards.

In the preparation of antipneumococcus serum, the type specificity of the strains as antigens is so marked that it has not been possible to prepare effective polyvalent serum. Early type diagnosis and the administration of the homologous serum are therefore essential.

In the preparation of antistreptococcus serum, not only must the type and toxin specificity of the strains be considered, but also the antigenic action, which varies. A serum of broad valence is essential since early type diagnosis is not practicable as in pneumonia. In the production of antitoxic serum it is now possible by the selection of two strains of hemolytic streptococci to obtain a serum of high potency and a valency so broad that it includes the toxins of practically all strains.

Preparation of all these sera has advanced to the point where it is now necessary to stress particularly the other side of the problem—namely, early diagnosis and early treatment with adequate dosage.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

THE COMPARATIVE VALUE AND THE LIMITATIONS OF THE TREPHINE AND PUNCTURE METHODS FOR BIOPSY OF THE STERNAL BONE MARROW *

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THE last few years have witnessed a striking development of interest in the sternal bone-marrow biopsy. This is undoubtedly due to at least two factors: the rapidly increasing interest in hematology which followed the discovery of the value of liver in pernicious anemia, and the increasing recognition that the so-called "blood diseases" are in reality disorders of the blood-forming organs, more particularly of the bone-marrow. Biopsy of the sternal marrow, introduced by Seyfarth [1] in 1923, rapidly displaced the much more difficult biopsy of the tibia which was practised by Zadek,[2] Peabody,[3] and a few others. The diagnostic value of the sternal bone-marrow biopsy particularly in cases presenting anemia, leukopenia, and thrombocytopenia has already been referred to in another paper.[4] The technic of the procedure consists in brief of the removal by trephine of a small plug of bone from the sternum. Two types of preparations are obtained: (1) *sections,* made by imbedding and cutting the small plug of bone removed, and (2) *smears,* made by touching gently bits of bone removed by curette from the trephine cavity. In the above paper and in another describing the appearance of the bone-marrow at biopsy in pernicious anemia,[5] the important features of both types of preparation were stressed, i.e. from the sections are obtained general ideas of the cellularity of the marrow, the topographical relations of various groups of cells, and the presence or absence of islands of embryonic cells. From the smears, careful study of the individual cells can be made, the cells appearing much as in a blood smear without the distortion and shrinkage frequently found in the sections. The definite impression has been obtained that in order to make a proper study of the sternal bone-marrow at biopsy, both the marrow sections and smears are essential, each type of preparation having its definite shortcomings and advantages.

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More recently another method for examining the sternal marrow has been introduced. In this method, a modified lumbar puncture needle is plunged into the sternal cavity and material obtained for smears by suctioning with a syringe. First introduced by Arinkin [6] and other Russian investigators, the method became widely practised, so much so that within the last few years two monographs (Segerdahl,[7] Nordenson [8]) have appeared based entirely on this procedure. A large number of articles extolling the ease of technic and the diagnostic value of the method have appeared.[9] As far as we know, there has been no critical appraisal of this method nor any comparison of the results with those obtained by the trephine method. The present paper, which deals with a critical examination of these questions, is based upon a comparison of the data obtained by both methods in 20 consecutive cases, together with a review of the pertinent data from about 200 previous biopsies.

Methods

Under aseptic precautions and following thorough infiltration of the skin and periosteum with novocaine, a small incision 1 to 2 cm. in length was made over the midsternum in the region of the fourth intercostal space. The periosteum was exposed, incised, and retracted in the ordinary manner. A puncture diagonally through the anterior lamella of the sternum was then made with a lumbar puncture needle which had been shortened to about one-half its regular size. When a sensation of " give " was obtained, the stilet was removed, and a very small quantity of material aspirated into a 20 c.c. syringe. Ordinarily, less than 0.5 c.c. of material was removed and this was spread gently on glass slides as with blood smears. Following this puncture, a small trephine was introduced into the sternum and a small plug of bone removed. This was immediately placed in Zenker's solution containing 5 per cent of glacial acetic acid sufficient for decalcification. The cavity resulting from the removal of the plug of bone was carefully scraped with a fine curette, bits of bone being removed which were then gently smeared on glass slides. Reticulocyte preparations were made with both the puncture and trephine preparations by using slides which had previously been coated with a thin film of cresyl blue (0.3 per cent brilliant cresyl blue in 95 per cent alcohol). Both types of smears were stained either with Wright's stain or with Giemsa stain and in several instances a combination of both stains was used. The Wright's stained preparations gave uniform results and presented delicate cellular pictures. The Giemsa stained preparations were more " brilliant " and showed better staining of the granules, although the nuclei were at times overstained. Differential counts of the " puncture " and the " trephine " smears were made, in both cases at least 500 cells being counted. Reticulocyte counts were made in most instances, 1000 non-nucleated erythrocytes being counted. The sections, after ap-

propriate fixation, were prepared in the ordinary way with paraffin and stained with eosin-methylene blue.*

STERNAL BONE MARROW BIOPSY
Trephine vs. Puncture Method

	Trephine	Puncture
1. The Smears—General Exam.	Normally highly cellular.	Frequently very few marrow cells.
2. Ratio Nucleated R.B.C. to W.B.C.	About 1 : 1.	Usually about 0.5 : 1.
3. Types of Nucleated R.B.C.	All types, including most primitive, present.	Primitive cells much diminished, often absent.
4. Reticulocytes	5–15%.	0.5–2%.
5. W.B.C.	Essentially similar findings.	———
6. Megakaryocytes	Common.	Infrequent.
7. Ease of Performance	Relatively difficult.	Easy—Amassing of data Serial observations Children.
8. Interpretation	Relatively easy, because both sections and smears obtained.	Smears only, often with more blood than marrow, make interpretation difficult.

The morphological characteristics of the various cells encountered in the marrow have already been described in previous papers. All cells were carefully studied from the standpoints of size, shape, cytoplasmic characteristics (amount, color, granules, vacuoles) and nuclear characteristics (size relative to cell, type of nuclear chromatin, nucleoli). The leukocytic cells discriminated were the histiocyte (hemohistioblast), myeloblast, promyelocyte, myelocyte, metamyelocyte, mature polymorphonuclear cell, eosinophile and basophile. Our nomenclature for the erythroblastic cells is based on previous studies in pernicious anemia and differs somewhat from that of other authors. The most primitive cell of this series is the erythrogone, which is found in all conditions in which the marrow is hyperplastic and is apparently the forerunner of both the megaloblast and the normoblast. In the absence of "liver extract substance" (pernicious anemia and related states), an abnormal or megaloblastic type of erythropoiesis takes place. Various grades of maturity of megaloblasts are seen and these may be arbitrarily classified as "A," "B," and "C."

When "liver substance" is present, normal red blood cells are formed, i.e. *normoblasts*. Similarly, three types of normoblasts are distinguished: "A," "B," and "C," corresponding to the terms frequently used in the literature of macroblast, erythroblast, and normoblast respectively.

RESULTS

A. The Smears. Differential counts from both types of preparations in 20 cases together with the ratio of nucleated red blood cells to white blood

* Best results in staining both smears and sections were obtained by using the Gruebler stains.

TABLE I

Biopsy Smears

				Normoblasts			W.B.C.								
		Eg	Meg	"A"	"B"	"C"	P	P 2 and 3	My-elo-cytes	Blasts	His-tio-cytes	L	E	Retics	RBC : WBC
1. Anthony P.	(*a*)*	4.2		13.1	26.4	15.0	9.6	18.2	10.7	0.7	0.3		1.8	7.2	1 : .75
	(*b*)†	0.4		0.2	1.2	39.9	12.8	35.7	6.9	0.4	0.2		2.3	2.6	1 : 1.38
2. Margaret B.	(*a*)	6.4	18.8	2.6	9.8	9.6	7.0	19.8	11.4	0.6	1.0	11.6	1.0		1 : 1.1
	(*b*)	5.2	14.0	0.6	9.2	8.0	12.8	22.6	14.0	1.8	—	8.8	2.4		1 : 1.7
3. Maria S.	(*a*)	7.2	9.6	3.0	9.9	16.8	8.1	19.2	11.1	—	—	14.1	0.9	16.7	1 : 1.15
	(*b*)	0.2	0.2		5.6	15.4	10.6	26.0	5.4	—	—	36.0	0.6	7.5	1 : 3.7
4. Catherine D.	(*a*)	—	—	3.0	12.8	14.2	6.0	34.2	18.4	6.0	3.2	2.4	2.4	9.6	1 : 2.3
	(*b*)	—	—	0.4	5.8	22.0	6.8	42.0	17.0	0.4	—	5.4	2.2	1.4	1 : 2.5
5. Margaret S.	(*a*)	6.7	19.2	—	1.0	2.5	7.0	21.7	19.2	4.5	1.5	12.5	4.7	9.2	1 : 2.4
	(*b*)	1.2	2.6	2.8	13.8	8.2	8.0	27.6	26.2	3.8	0.6	3.2	2.0	5.7	1 : 2.5
6. Catherine S.	(*a*)	1.1	—	4.2	9.9	15.0	9.8	25.6	11.5	4.8	—	17.0	6.9		1 : 2.5
	(*b*)			4.8	15.8	7.0	9.7	23.7	9.7	0.2	0.2	21.4	7.4		1 : 2.6
7. Frank C.	(*a*)	0.2	—	4.8	21.8	10.0	6.6	25.6	18.6	1.0	0.4	7.6	3.4	5.2	1 : 1.7
(Poor in cells)	(*b*)	—		1.5	6.5	4.5	17.5	44.5	12.5	—	—	12.0	0.5	1.9	1 : 6.8
8. John F.	(*a*)	—	—	0.4	19.0	15.6	4.4	27.6	21.2	3.4	1.2	5.4	1.8	4.7	1 : 1.7
	(*b*)	0.8		3.8	12.2	8.8	6.8	31.0	14.6	3.2	1.6	13.8	3.4	0.8	1 : 3.1
9. Swan A.	(*a*)	9.0	30.6	1.6	9.8	5.8	9.8	10.0	9.4	1.6	0.2	3.0	9.2	5.4	1 : .87
	(*b*)	2.5	13.0	2.7	10.1	15.6		25.2	9.4	1.6	0.2	17.4	1.8	18.7	1 : 1.3
10. Christine Y.	(*a*)			5.2	23.4	10.8	6.2	20.6	17.4	3.0	1.0	9.8	2.6	3.7	1 : 1.3
(Poor in cells)	(*b*)			1.4	9.2	6.7	19.4	30.6	12.7	1.1	0.3	17.2	1.4	1.1	1 : 4

* (a) = Smears from trephine curettings.
† (b) = Smears from puncture material.

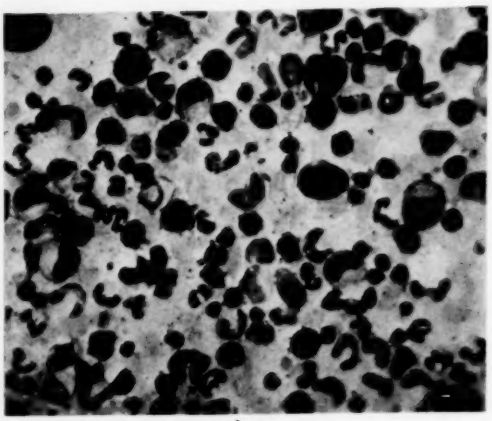
TABLE I—*Continued*

* (a) = Smears from trephine curettings.
† (b) = Smears from puncture material.

TABLE I—*Continued*

				Normoblasts			W.B.C.								
		Eg	Meg	"A"	"B"	"C"	P	P 2 and 3	Myelocytes	Blasts	Histiocytes	L	E	Retics	RBC : WBC
11. Hugh McG.	(*a*)	9.7	23.3	2.1	4.5	5.5	8.8	16.0	10.2	1.7	1.8	13.6	2.0	3.9	1 : 1.22
	(*b*)	7.8	10.0	8.0	10.6	9.4	12.4	24.8	11.4	1.0	1.2	7.8	2.8	5.1	1 : 1.3
12. James L. (Poor in cells)	(*a*)	0.8	—	10.4	33.6	4.8	3.4	19.0	12.4	1.0	0.4	11.0	3.2	7.8	1 : 1
	(*b*)	0.8	—	3.6	17.2	7.2	7.4	35.0	14.6	0.6	—	10.6	2.4	4.6	1 : 2.5
13. Armin L.	(*a*)				1.4	7.8	0.8	2.0	0.2	83.8	1.0				1 : 9
	(*b*)				4.6	7.8	2.4	1.4	0.2	79.8	0.8	2.8			1 : 8
14. Fred T.	(*a*)	0.8		8.9	21.9	7.3	7.4	19.7	16.9	1.4	2.7	10.5	2.5		1 : 1.6
	(*b*)	0.6		4.8	12.8	4.6	13.8	30.6	11.8	1.4	0.4	16.0	3.2		1 : 3.4
15. Nathan W.	(*a*)	0.2		2.6	17.2	10.6	11.0	32.2	13.8	1.0	0.4	7.0	4.0	6.5	1 : 2.3
	(*b*)	0.4		4.0	11.4	3.6	12.4	36.0	17.4	1.2	2.4	8.0	3.2	3.0	1 : 3.0
16. Barbara W.	(*a*)	9.2		12.6	11.4	8.0	5.6	15.2	19.0		0.8	15.6	1.6		1 : 1.4
	(*b*)	2.0		17.2	7.0	1.2	24.6	23.4	7.8	2.0	0.4	10.2	2.8		1 : 1.4
17. Abraham L.	(*a*)	0.8		3.4	9.6	45.0	4.4	22.6	12.4	1.0			0.6		1 : .67
	(*b*)	1.2		5.0	17.2	13.0	12.0	36.6	7.4	1.0	0.2		0.6		1 : 1.50
18. Zalman K.	(*a*)	2.3		4.3	24.3	23.7	1.3	22.0	16.7	4.0	Many Gaucher cells seen.				1 : 0.8
	(*b*)	0.4		4.0	15.4	9.0	6.8	23.0	18.2	8.8	6.4 Few Gaucher cells.		8.0		1 : 3.4
19. Arthur MacA.	(*a*)	14.0	49.6				5.7	18.6	9.3	0.8					1 : 0.6
	(*b*)	2.8	33.0				15.0	24.2	24.2	0.8					1 : 1.8
20. Harrison L.	(*a*)	2.0		8.2	26.8	38.6	3.4	9.0	.4	.3		7.4	1.4		1 : .33
	(*b*)	1.0		4.2	13.6	20.6	16.6	18.8	3.4	4.6		15.8	.6		1 : 1.5

* (a) = Smears from trephine curettings.
† (b) = Smears from puncture material.



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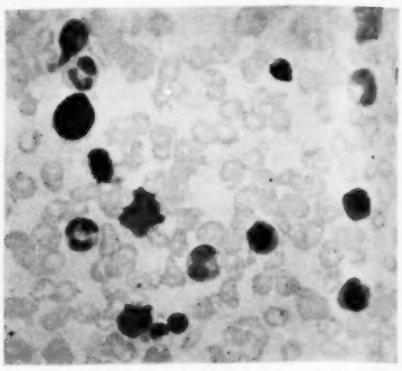

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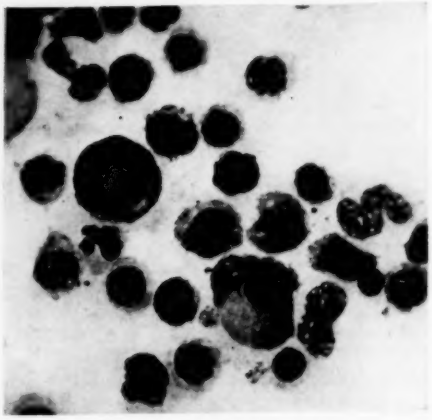

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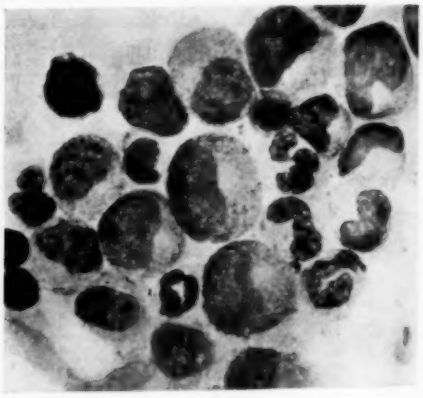

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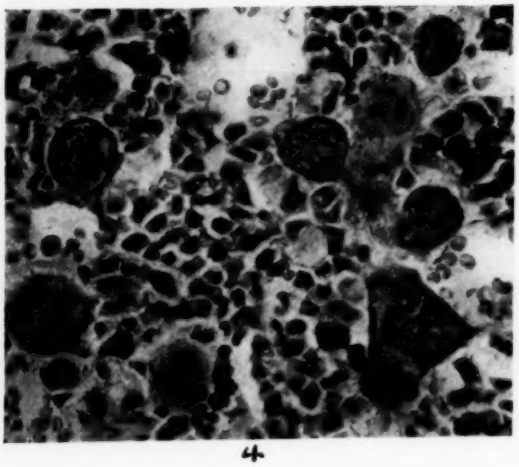

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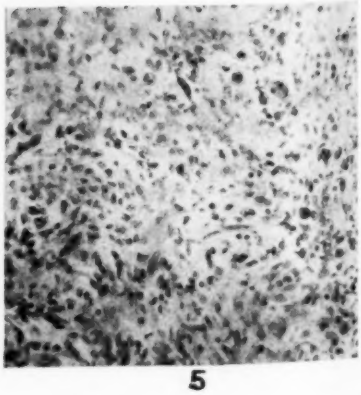


5

cells, and the reticulocyte counts are presented in table 1. In three cases, the " puncture " smears were very poor in cells, making differential counting difficult if not impossible. This has frequently been our experience in other cases when only puncture was done and the same is noted in many of the protocols of both Nordenson [8] and Segerdahl.[7] In the " trephine " preparations, except in those cases with an acellular marrow, highly cellular preparations were always obtained. In the " puncture " preparations, the cells obviously arising from the marrow were relatively scanty as compared with the numbers of mature erythrocytes in the preparations, so that the picture usually resembled closely a blood smear either from a case showing leukocytosis or leukemia. Differential counting in these preparations was at times somewhat easier than in the " trephine " preparations in which the cells might be closely packed together, but one obtained the definite impression that in the one case one was dealing with blood containing a few marrow cells whereas in the other one dealt with marrow interspersed with some blood cells.

Ratio of Nucleated Red Blood Cells to White Blood Cells. This ratio, which from previous studies had generally been found to be about 1 to 1 (with variations from 0.6 to 1 to about 1.5 to 1) is useful in estimating whether the granulocytic or erythroblastic cells predominate in a given preparation. It may be seen from the table that, although the ratio of red cells to whites was frequently substantially the same in both types of preparation (Cases 4, 5, 6, 11, 13, 16), in 14 cases it was different. In each of these cases, the ratio of nucleated red cells to white cells was definitely less in the puncture preparations. In several cases, the preponderance of white cells to reds in the puncture preparations was quite striking (3, 7, 8, 10, 14, 15, 18). These findings may be interpreted as signifying the failure of the primitive red cells to appear in large number in the " puncture " smears as noted below.

From table 1, one sees that in seven of the 20 cases, the most immature nucleated red cells (erythrogones, megaloblasts, normoblasts " A," " B ") in the " trephine " preparations far outnumbered the same types of cells in the puncture preparations. In several cases the results obtained in the " puncture " preparations might well have been misleading in this regard. In Case 3, for example (pernicious anemia), megaloblasts were present in

FIG. 1*a*. Sternal bone-marrow biopsy smear. Made directly from a bit of bone removed by trephine-curette method. Note large numbers of marrow cells present. × 500.

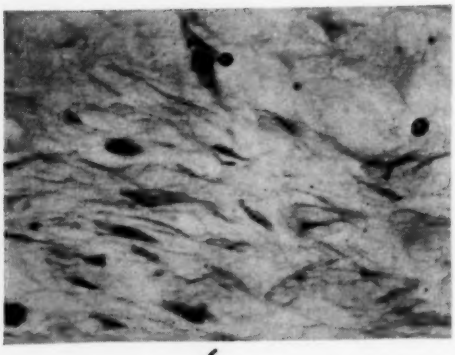
1*b*. Smear. Made from puncture biopsy in same case. Note the scarcity of marrow cells and the large number of blood cells. × 500.

2. Trephine biopsy. Smear. Various types of nucleated red cells are seen. The smears are invaluable for study of individual cellular morphology. × 1000.

3. Trephine biopsy. Smear. Various types of granulocytes are seen. × 1000.

4. Trephine biopsy. Section. Polycythemia illustrating marked hyperplasia of megakaryocytes. Megakaryocytes are found only occasionally in puncture preparations. × 550.

5. Trephine biopsy. Section. Aleukemic reticulosis. The marrow is replaced by dense tissue. Smear preparations were worthless since they showed no cells. × 125.



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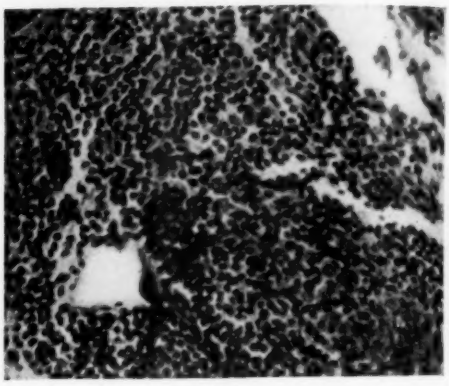

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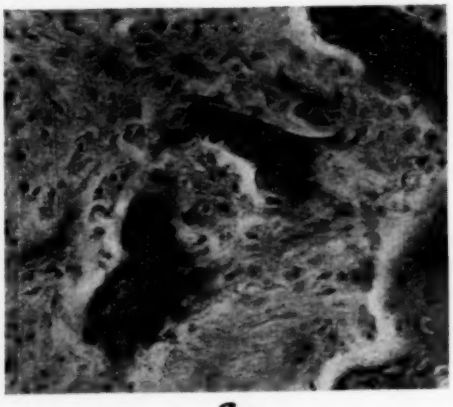

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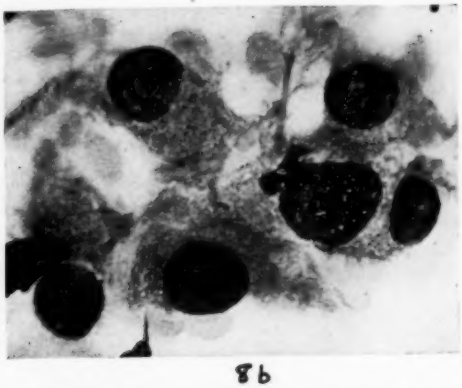

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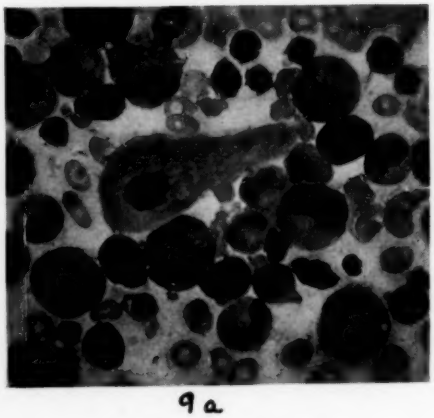
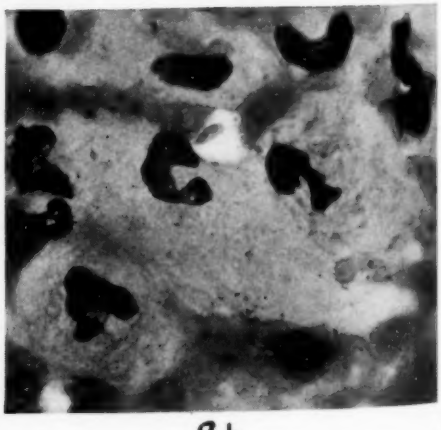


9a



9b

fair number in the trephine preparations and almost completely absent from the puncture preparations.

Reticulocyte Percentage. This was used as an index in demonstrating the relative maturity of the non-nucleated red cells in the trephine as compared with the puncture preparations and was determined in 11 cases. In nine of these the percentage of reticulocytes was greater in the trephine preparations, although in two cases (9 and 11), both of them examples of pernicious anemia under treatment, the reticulocyte per cent was greater in the puncture preparations.

White Cells. Although rather marked differences in the percentage composition of the white cells were present at times, no such striking disproportion between immature and mature leukocytes as existed with the erythroblastic cells could be seen, although in two cases (4 and 6) the percentage of myeloblasts in the trephine preparations was much higher than in the puncture preparations.

Megakaryocytes. These huge cells were commonly found in the trephine preparations, being seen only occasionally in the puncture preparations.

B. The Sections. These were of course present only with biopsy preparations. Although artificial sections may be prepared from the puncture preparations by allowing the puncture material to clot and then sectioning it in the ordinary way, these were not made. As brought out in previous papers,[4, 5] the sections are of value not so much for the examination and study of the individual cells as for the study of the topography of the marrow and its general functional state (hyperplasia, hypoplasia, etc.), the recognition of islands of proliferating leukemic or malignant cells, the relationship of islands of cells to each other and to adjoining reticulo-endothelial cells and for study of the megakaryocytes.

Smear preparations, particularly those obtained by puncture, may show varying degrees of cellularity dependent wholly upon differences in technic. These differences may be so great that the distinction between hypoplasia and hyperplasia may be impossible. Thus, in Case 17 (benzol poisoning), the smears from both the biopsy and puncture preparations seemed to show an essentially normal number of cells, and yet the sections (figure 10) showed a striking degree of hypoplasia of most of the marrow with small islands of fairly normal cellularity. In Cases Mary C., Mitchell G., Edna S., Charles

FIG. 2. 6. Trephine biopsy. Section. Lymphosarcoma of spleen; metastasis to bone-marrow with fibrous tissue replacement. The smear preparations showed no cells. × 500.

7. Trephine biopsy. Section. Lymphosarcoma; metastasis to bone-marrow. Dense mass of tumor tissue present in one small area of section, not discovered in smear preparations. × 300.

8*a*. Trephine biopsy. Section. Metastatic carcinoma of pancreas. Bone-marrow replaced by fibrous tissue. No malignant cells seen. × 300.

8*b*. Trephine biopsy. Smear. The smears (same case as 8*a*) showed groups of primitive cells thought to be carcinoma. This was later confirmed by post-mortem examination. × 1000.

9*a*. Puncture biopsy. Smear. Splenomegaly ? cause. Smears showed normal marrow cells with a rare large cell called a histiocyte. × 1000.

9*b*. Trephine biopsy; same case. Smear. Large numbers of Gaucher cells present in the smears and sections making diagnosis readily possible. × 1000.

TABLE II

Smears and Sections

	Smear Preparations	Sections
Mary C.	Diminished cellularity	Islands of leukemic cells
Mitchell G.	No cells	Connective tissue replacement of marrow (lymphosarcomatosis)
Edna S.	No cells	Aplasia of marrow
Charles M.	Very few cells	Replacement of marrow by reticulum and connective and proliferating reticulum cells with giant cells (aleukemic reticulosis)
Eva S.	Very few cells	Small localized area of lymphoblastic proliferation (lymphosarcoma)
Jacob H.	Very few cells ? Islands of abnormal cells	Metastatic malignancy (carcinoma of pancreas) with connective tissue replacement of parts of marrow
Sylvia W.	Hyperplasia of W.B.C. *Diagnosis:* Myeloid leukemia	Cellular bone-marrow ("Banti's disease")
Bessie D.	*Diagnosis:* Myeloid leukemia (Proliferation with primitive cells)	Hyperplastic bone-marrow, no unrestrained growth, islands of primitive cells surrounded by typical nucleated R.B.C. *Diagnosis:* Pernicious anemia
Maria B.	Hyperplasia of myeloblasts. *Tentative Diagnosis:* Aleukemic myelogenous leukemia.	Diagnosis confirmed by sections which showed islands of proliferating myeloblasts with invasion and destruction of R.B.C. and megakaryocytes
Isadore L.	Normal marrow	Hypoplastic marrow with small areas of normal cellularity. No megakaryocytes. *Diagnosis:* Hypoplastic anemia (benzol poisoning)

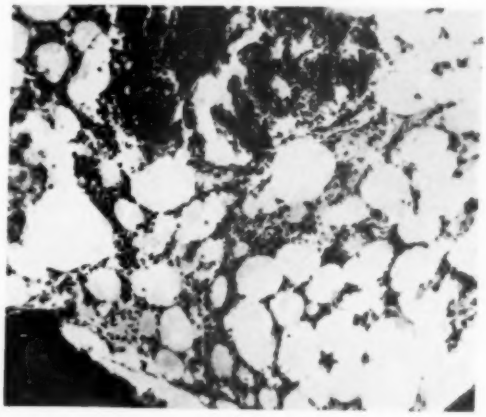
M., Eva S., Jacob H. (table 2), very few marrow cells were found in the smear preparations. All of these cases presented anemia, leukopenia, and thrombocytopenia, and it was impossible to state at the time whether the absence of cells was due to faulty technic or to actual aplasia of the marrow. It was only when the sections were studied in these cases that the true pictures became evident: myeloid leukemia; fibrosis of the marrow following lymphosarcomatous invasion; aplasia; aleukemia reticulosis; lymphosarcoma invading the marrow; carcinomatous invasion, and fibrosis of the marrow.

When dealing on the other hand with an obviously hyperplastic marrow in the smear preparations, it is at times difficult to state definitely whether or not leukemia is present. Occasionally (Cases Sylvia W. and Bessie D. are illustrative) the diagnosis of myeloid leukemia had been made on the basis of apparently extreme myeloid hyperplasia. The sections, however, in the first case showed normal, although hyperplastic, islands of both red and white cells without destruction or replacement of erythroblastic or mega-

karyocytic elements ("Banti's disease"). In Case Bessie D., the very primitive erythroblastic cells present (erythrogones) were mistakenly called myeloblasts; the sections showed islands of primitive cells, at the edges of which were easily recognizable erythroblastic cells: i.e. pernicious anemia. However, from sections alone, it is usually difficult if not impossible to distinguish between leukemia and pernicious anemia since both show large islands of primitive cells.

Comment

1. *Diagnostic Value of the Sternal Bone-Marrow Biopsy.* During the past ten years, ample proof has accumulated of the diagnostic value of the



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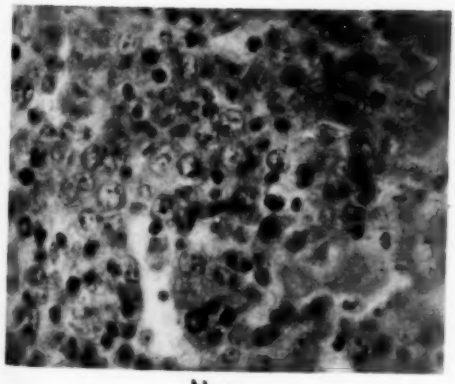
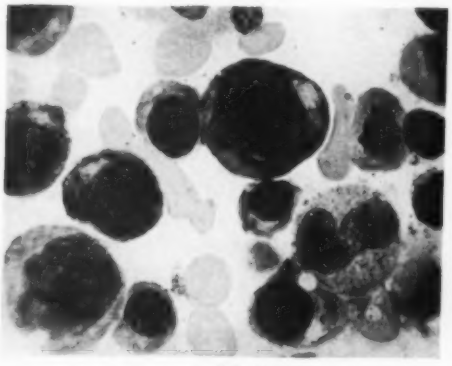


11 a



11 b

Fig. 3. 10. Trephine biopsy. Section. Hypoplastic marrow from chronic benzol poisoning. Diagnosis made when bone-marrow findings were discovered. Smears from both the puncture and trephine biopsies showed essentially normal findings. Sections invaluable for topography and general idea of cellularity. × 100.

11*a*. Trephine biopsy. Section. Extremely hyperplastic marrow with many primitive cells erroneously diagnosed as myeloid leukemia. × 500.

11*b*. Trephine biopsy; same case. Smear. The smears showed many megaloblastic cells and deformed metamyelocytes typical of pernicious anemia. The smears are essential for study of individual cellular morphology. × 1000.

sternal bone-marrow biopsy. Its chief use has been in the differential diagnosis of those cases presenting obscure and chronic anemia refractory to liver and iron. Usually these cases are associated with leukopenia and thrombocytopenia. This triad of hematological findings—anemia, leukopenia, and thrombocytopenia—may be due to many different conditions of the marrow. Thus, the marrow may be almost completely destroyed by chemicals (benzol, gold, etc.), i.e. aplastic anemia, or by proliferating malignant or leukemic cells, or may be extremely hyperplastic as in pernicious anemia, aleukemic myelogenous leukemia, spleen-liver (Banti's) disease, and yet the blood picture may be substantially the same. The frequent cases of leukemia with a low leukocyte count ("aleukemic" leukemia) have been a source of continued interest. Although many of these cases show very abnormal differential leukocyte pictures with the presence of primitive cells (lymphoblasts, myeloblasts, or histiocytes), not infrequently proved cases of leukemia show no changes whatever in the differential picture and are usually accompanied with an erythrocyte picture resembling pernicious anemia. Macrocytic anemia may be present not only in the "liver deficient" states (pernicious anemia) but in many other totally unrelated conditions: certain cases of hepatic disease, myxedema, chronic nephritis, leukemia, lymphosarcoma invading the bone-marrow, and in chemical destruction of the marrow. Usually leukopenia and thrombocytopenia are also present. The bone-marrow biopsy is especially helpful in unravelling the diagnosis in these cases and may show either a "full" marrow or a relatively "empty" one. In many cases it has been impossible to predict from the blood picture and the clinical findings whether the marrow will be hyperplastic or aplastic, so that in certain cases considered to be aplastic anemia, leukemia or lymphosarcoma will be found, and when pernicious anemia is suspected a hypoplastic marrow may be discovered. In six cases the anemia, leukopenia, and thrombocytopenia were due to widespread involvement of the marrow by lymphosarcoma. It is felt, therefore, that when a patient presents chronic anemia accompanied usually with a lowering of the leukocyte and platelet counts, and is refractory to liver and iron therapy, a bone-marrow biopsy may help to clear up the diagnosis.

2. *Critique of the Puncture Method; Limitations of Both Methods.* The phenomenal increase of interest in the study of the bone-marrow may be attributed to the rapidly growing interest in the so-called blood diseases and in the knowledge that fundamentally these represent disorders of the blood-forming apparatus, chiefly the marrow. So intense has this interest become in the last few years that various short-cuts have been utilized in the attempt to obtain information as expeditiously as possible. One of these short-cuts has been puncture of the sternal bone for the removal of material which has been called marrow.

The bone-marrow biopsy was first performed by Ghedini [10] in 1908, trephining of the tibia being done. This method languished for many years, only a few investigators, chiefly Zadek [2] and Peabody,[3] being bold enough

to continue drilling into such a heavily protected marrow. Furthermore, the tibial marrow was normally acellular and gave information only in such hyperplastic conditions as pernicious anemia. Trephining of the sternal bone as a much simpler maneuver was introduced by Seyfarth [1] in 1923 and was then slowly taken up. Custer and his co-workers [11] set up certain standards in biopsy of the sternal marrow such as those relating to comparison of its cellularity with that found in other bones. Puncture of the marrow with a hollow needle as introduced by Arinkin [6] and as modified by many workers has aroused great enthusiasm. This is indeed laudable since it indicates a greater interest in the marrow than was previously present but it also calls for some warning as regards interpretation.

As Custer [11] has pointed out, it is often dangerous to conclude from examination of a small piece of bone and marrow removed from the sternum the condition of the entire marrow which in size probably compares with that of the liver. In a scattered organ like the marrow, local conditions vary tremendously. This criticism must hold even greater weight for the material removed by puncture of the sternum with a hollow needle. This material looks very much like blood when aspirated; when smeared, it is found to consist mainly of mature red cells with a variable number of marrow cells, dependent both upon local conditions in the bone and marrow examined and on the technic. The first 0.5 to 1 c.c. contains many more marrow cells than the remainder of the aspirated material, so that several authors warn against removal of more than 1 c.c. Some investigators prefer to remove only sufficient material with which to make a few smears.

That the material removed by aspiration is mostly blood is confirmed by comparison of the "puncture" smears with the "trephine" smears made directly from bits of bone removed by curette from the trephine cavity. These show, as brought out above, that the ratio of nucleated red cells to whites is usually far greater in the trephine preparations, that the reticulocyte percentage is almost always much greater, and that the relative proportion of immature nucleated red cells is usually much greater in the trephine preparations. These observations suggest a number of interesting points some of which have already been emphasized; namely, that the nucleated red cells are intravascularly situated, the white cells growing extravascularly; that the more primitive nucleated red cells tend to remain adherent to the underlying endothelial surfaces, making them difficult to remove by simple aspiration. This is confirmed by the experiments of Maximow [12] who was unable to remove the most primitive erythroblasts from the marrow even by repeated perfusion. The same explanation probably accounts for the fact that the white cells greatly outnumbered the nucleated reds in the great majority of the puncture preparations. The comparative reticulocyte count may be used as an index of the degree of dilution of the immature cells with blood cells. The fact that the reticulocyte count (except in two instances of pernicious anemia under treatment) was always higher in the "trephine" than in the "puncture" preparations suggests that the puncture material is

obtained from a "part-way station" located between the bone-marrow on the one hand and the blood on the other. It would therefore seem improper to label the material removed by sternal puncture as bone-marrow since it appears to be chiefly blood in which are present a variable number of marrow cells. "Marrow juice" might be a better term.

Other criticisms of the technic of puncture have already been mentioned above. These are perhaps more important from a practical standpoint than those just discussed; namely, that the puncture material gives no idea of the topography of the marrow, that it is frequently deficient in cells when the marrow is cellular, that the deficiency in cells may be incorrectly interpreted when the marrow has become fibrotic as the result of previous invasion by tumor or leukemia, that it may fail to show Gaucher cells, leukemic islands, or small masses of proliferating metastatic cells, and that the interpretation of a hypoplastic or hyperplastic marrow is frequently impossible.

The criticisms of the puncture technic should not prevent us from conceding to it its relative simplicity and ease of technic as compared with the relatively formidable technic of trephination. Aside from ease of technic, it has certain obvious advantages: its applicability to infants and small children and its use for several examinations of the marrow in a case under continued treatment or observation. We feel, however, that once the idea of biopsy of the marrow has been entertained, it should be accomplished by as good a method as we have at our disposal rather than to rely upon the more or less haphazard results obtained from puncture despite its simplicity.

From the foregoing, the impression should not be obtained that the bone-marrow biopsy when performed by the trephine method which we have utilized must always give perfect results. As with all diagnostic methods, errors may be made. These are ordinarily due to poor preparations which are occasionally obtained, or to incorrect interpretations. The findings in the marrow may be stretched to make a preconceived diagnosis. Experience, and particularly the bitter ones of demonstrated error, have led us to postpone a definite diagnosis unless both the sections and smears have been examined and correlated; this inevitably means a delay of several days for the sections, but this amount of patience has been found valuable. In the absence of either the smears or the sections or of good preparations, it is advisable to hedge on the diagnosis, unless the condition is clear-cut. The smears are of no value when the marrow is extremely hypoplastic or fibrotic. The sections, however, may mislead us into making a diagnosis of leukemia as, for example, in the extreme hyperplasia of pernicious anemia with the presence of large numbers of primitive cells and many mitotic figures. Study of the bone-marrow when dealing with large sections from autopsies is difficult enough; with the small bits of marrow removed from the sternum at biopsy, it is advisable to keep one's diagnostic enthusiasm in close check. It is gratifying to note that with continued attention to these points our percentage of errors has been diminishing materially from year to year. With due attention to details, with proper preparation of both the smears and

sections, and above all with proper interpretation of what is seen, the biopsy should well repay the effort entailed in its execution. The data obtained from puncture material must always be surrounded with reservations since they are based on the findings in a fluid of uncertain origin and of mixed content. For research study, as Jaffé has pointed out,[13] the puncture biopsy is certainly not to be relied upon.

3. *Indications for Sternal Bone Marrow Biopsy.* The most obvious and important indication for sternal biopsy is in the diagnosis of obscure hematological problems, particularly in cases presenting persistent anemia, leukopenia, or thrombocytopenia, either singly or in combination. Because the biopsy is a surgical procedure, although a simple one, it stands to reason that all the various other diagnostic methods of probable value should first be carried out. The diagnosis of a case presenting obscure long-standing anemia may lead one into all sorts of by-ways far afield from what is technically hematology, but this simply illustrates that this field cannot be divorced from clinical medicine, of which it is an integral part. When complete physical examination, studies of the blood, roentgen-rays of the chest, the gastrointestinal tract, and the bones have not been productive of a diagnosis, the sternal biopsy may solve the problem. One should, however, be prepared for disappointment, for occasionally even this procedure fails to clear up an obscure case.

Knowledge of the condition of the marrow may at times be essential preliminary to the serious operation of splenectomy. Is a given case "Banti's disease," warranting splenectomy, or is it aleukemic myelogenous leukemia which is best left alone? In a recent case presenting severe rapidly progressive macrocytic anemia, splenomegaly, icterus, a normal fragility test, and lack of response to liver extract, it was important to know whether the marrow was merely hyperplastic or showed invasion by leukemic or malignant cells. When only extreme normoblastic hyperplasia was found, the operation of splenectomy was done and was followed by a spectacular recovery. Lawrence and Knutti [14] have pointed out that it might be worth while to note the condition of the megakaryocytes in a case of thrombocytopenic purpura prior to splenectomy since if the marrow were found to contain large numbers of these cells, the operation would probably prove successful; if megakaryocytes were few, splenectomy might be of no value. Splenectomy is occasionally done for "aplastic" anemia; it seems wise to be sure of one's ground before this major operation is done. The caution should be made that in the presence of a very low platelet count the biopsy should be performed with unusual care and possibly postponed until after a transfusion of blood is given.

Another indication for sternal biopsy is in the differential diagnosis of splenomegaly. Seyfarth, who originated the method while stationed at an institute of tropical medicine, first used it in the diagnosis of chronic malaria and kala-azar. He felt that the procedure did not carry with it the dangers of splenic puncture, with possible rupture of the capsule and resultant hemor-

rhage. This possibility has also deterred us from utilizing the latter diagnostic method, although such observers as Pittaluga [15] have performed splenic puncture without accident in several hundred cases. The diagnosis of Gaucher's disease which may present splenomegaly as the only abnormality has been alluded to above. The spleen and the bone-marrow are so closely interrelated that study of the marrow may thus yield valuable information regarding the more inaccessible organ.

A final indication for the sternal bone-marrow biopsy is in the research study of various hematological problems, the ultimate rationale being the gradual development of knowledge regarding their physiological pathology. Studies of this type have already added to our understanding of the effects of liver therapy in pernicious anemia, and of aminopyrine in producing maturation arrest in agranulocytosis.[16] Many other problems remain to be worked out. Again, the hope is expressed that hit-or-miss methods should not be tolerated.

Summary and Conclusions

The diagnostic value, indications, and limitations of the sternal bone-marrow biopsy were discussed. In 20 consecutive cases, the trephine and the recently popularized puncture methods for biopsy of the sternal marrow were compared. With use of the trephine, two types of preparations are obtained: sections made from the removed plug of bone, and smears made from bits of bone removed from the edges of the trephine opening. With the puncture, a sanguinous appearing material is aspirated, from which only smears can be made.

A comparison of the smears made with the "trephine" and the "puncture" methods showed a far greater cellularity in the biopsy preparations, a greater reticulocyte percentage, a greater number of erythroblastic cells relative to granulocytes, and a greater number of early nucleated red cells. The puncture preparations frequently consisted almost entirely of red blood cells interspersed among which were some marrow cells. The sections obtained at biopsy not only gave one an idea of the general topography of the marrow, but of its general degree of cellularity, the presence or absence of islands of leukemic or neoplastic cells, and in certain cases of connective tissue replacement. Combined study of the sections and of the smears has proved to be of much greater value than study of the one type of preparation alone.

Puncture biopsy of the sternum is to be criticized because the material obtained is usually not marrow but a variable mixture of blood with marrow cells ("marrow juice"); because lack of cellularity in this aspirated material does not necessarily mean lack of cellularity in the marrow itself; because primitive erythroblastic cells, present in the marrow, are frequently not obtained; and because abnormal islands of neoplastic and leukemic cells are either not obtained or if seen may be misinterpreted because of the lack

of topographical relationship. The chief advantage of puncture biopsy is its simplicity, but this is greatly outweighed by its inaccuracy. When the procedure of bone-marrow biopsy is contemplated, we feel it should be done in as careful a manner as possible since, even with the best technic, interpretation may be difficult.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

NEUROLOGIC MANIFESTATIONS IN "HYPOGLYCEMIC SHOCK" (SAKEL) *

By LEWIS A. GOLDEN, M.D., *New Orleans, Louisiana*

PRESENT attempts to treat schizophrenia and other psychoses with hypoglycemia induced by large doses of insulin, afford the opportunity of observing at one's leisure, many interesting neurological manifestations seldom otherwise witnessed.

Through the courtesy of Dr. John R. Ross, Superintendent of the Harlem Valley State Hospital, N. Y., and the kindness of Drs. I. Murray Rossman, William B. Cline, Jr. and O. Schwoerer of the male service and Dr. A. Goulacher and Dr. Pellens of the female service I was among those privileged to observe this phase of their work on the "Insulin Wards." The method used was that of Sakel who had personally trained the staff during his stay at the Harlem Valley State Hospital. Their scientific and conservative attitude left a lasting impression of the reliability of their evaluation of the treatment, which we hope will soon be published. We witnessed most encouraging results in a group of patients characterized by Dr. Sakel himself as "deadwood" and offering little expectation of improvement. I am sure that these interesting results will be reported in detail by those in charge of the work at a later date.

Many of the manifestations which accompanied the hypoglycemic state were of particular interest to the neurologist. These neurological pictures were so varied and striking in their combination and appearance that in all probability they are now being seen for the first time in this condition of severe hypoglycemia. In my experience, none of these have been described in accidental hypoglycemia arising as a complication of diabetic treatment or as a symptom of pancreatic adenoma.

I found it useful for my own comprehension of these complicated neurologic events to arbitrarily divide them into three categories, namely:

(1) "Prolonged" manifestations which were those occurring for a longer period during the four to five hours of treatment;

(2) "Sudden" manifestations which were those which occurred suddenly and usually toward the end of the treatment.

(1) The "prolonged" manifestations:

Soon after the insulin had been given, the patient ordinarily remained quiet and resting. During the second hour, when diaphoresis usually was well established, there would ensue either somnolence, restlessness, mild

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excitement, or shouting. This usually passed off as the hypoglycemic state progressed into deeper coma. In this phase one could observe:

(*a*) Quick, jerking movements of the arms, legs, body, and restless tossing of the head. A sudden flexion, but less frequently extension of both arms was extremely common. These movements often recurred for an hour or more during the treatment and as often as 15 to 20 times per minute, although the rate varied greatly. Touching or shaking the patient frequently initiated such " flexor arm jerks."

(*b*) Some patients exhibited prolonged sucking movements of the lips. No special emotion could be noted in the facial expression during these movements. At times, there was marked grimacing of the face accompanied by bilateral athetoid movements of the extremities.

(*c*) There were episodes initiated by flushing of the face, dilation of the pupils and labored breathing. These were associated with rigid extension of the lower extremities, bilateral adduction and extreme internal rotation of rigidly held arms. The wrists were rotated to hold the palms outward. The fingers were most often tightly clenched into the palm with the thumb projecting characteristically between the index and middle finger, or the ring and middle finger. The eyelids were often retracted widely, producing a picture of extreme fright. The whole movement was slow and rhythmic. After about thirty seconds to one minute the arms and legs would relax and resume a neutral position until the next movement began again. This picture at its climax, clinically suggested the attitude of decerebrate rigidity.

(*d*) There occurred at times only a partial manifestation of the above. The arms would rotate, the palms face outward, but the limbs would remain fairly well relaxed and this position would be maintained for long periods without any interruption.

(*e*) Irregular, thrashing, apparently purposeless movements of the arms and legs were frequently noted. At times there seemed to be definite attempts to brush away the physician's arm or the towel on the patient's forehead. These movements suggested true defense reflexes. The patient would often strike the bed, the wall, or his own face during this activity.

(*f*) The deep reflexes were difficult to evaluate because of the constant spasms in the extremities which interfered with their elicitation. However, following the somnolent stage, the Babinski reflex would appear and then become sluggish as the patient approached deeper coma. The corneal reflex also disappeared in the later stages of coma. More often the Babinski appeared as part of a general flexor withdrawal reflex but toward the deeper stages of coma it could be elicited alone before its final disappearance in deepest hypoglycemia. Its appearance or disappearance apparently mirrored the depth of the hypoglycemic shock.

(*g*) Slow " trombone like " movements and irregular jerks of the tongue often were seen. A spontaneous clonus of the lower jaw, and clonic movements of the upper eyelids sometimes appeared for a short while.

(*h*) The extremities sometimes assumed a posture resembling that seen during the movements of dystonia musculorum or athetosis; however, they remained fixed in these positions, suggesting the term "frozen athetoid movements" for their description. Dr. Dussik told me of seeing true hemiballistic movements as well as athetoid position of the hands in his Vienna material.

(*i*) Transitory hemiplegias sometimes occurred. Drs. Cline and Schwoerer told me of seeing a hemiplegia which lasted for nine hours. I observed several transitory hemiplegic states. In one instance, a case on Dr. Goulacher and Dr. Pellens' service showed a transitory palsy of the left side of the face which preceded an epileptic convulsion.

All the movements and postures just described were most often bilateral but at times unilateral.

(2) "Sudden" neurologic manifestations:

(*a*) Convulsive seizures frequently occurred and could be clearly recognized from the other convulsive movements of a more prolonged character in most instances. It was often difficult for me to decide exactly when a series of convulsive movements could be grouped as a seizure. The definition of what constitutes a true epileptic seizure is still highly unsatisfactory. Certainly if we call mild disturbances of consciousness with slight twitching a petit mal attack in everyday medicine, it then becomes quite difficult to state that a series of severe convulsive movements in an unconscious patient is not a true epileptic seizure. Sakel himself uses the term in a rather indefinite way, and so do many others.

(*b*) There occurred in about a dozen instances according to the doctors a sudden dramatic complication usually toward the end of the treatment, one of which I witnessed. Three cases were of great severity while the others were said to have been milder. These alarming manifestations of such a severe complication were particularly frightening to the onlooker when seen for the first time. Drs. Rossman, Cline and Schwoerer felt that their observation may represent a specific type of complication with special prognostic features. Dr. Dussik stated that in his experience it had occurred only five times in about 5000 treatments. It usually appeared as follows: When the regular proceedings for the termination of the hypoglycemic state had been instituted, the patient would fail to react. By previous experience the doctors had found that if such a patient did not react in 45 minutes even when intravenous glucose had been given, trouble was in all probability to be expected. The patient at the time was often noted to have very small pupils, which then slowly dilated and were associated with marked flushing of the face. There then ensued an excited phase with convulsive movements, contortions, rigid attitudes and extremely labored breathing lasting for 15 to 20 minutes. This phase was so severe that the patient appeared to be in extremis and completely exhausted. The movements would then slowly subside in severity and duration, the pupils return to more normal size, and the patient relax in apparent exhaustion

with shallow slow respiration. After a lapse of 10 to 20 minutes another active phase would begin, augment to a frenzy of labored irregular movements and again subside. These alternating periods of activity and relaxation at times continued for one to two hours, diminishing in duration and severity with each attack.

It seemed as if the whole central nervous system was thrown into a frenzy of disorganized activity. There were recognizable hemiplegic attitudes, extrapyramidal manifestations of transitory cog-wheel rigidity, and signs of midbrain involvement in disturbed extraocular movements—the eyeballs moving asynchronously. There were also signs suggestive of disordered thalamic and medullary control of temperature, pulse and respiration, which appeared entirely disassociated from their usual relationship. For example, the temperature being 104.2° F., the pulse would be 160 and the respirations as high as 80 per minute. There were in addition manifestations of overactivity at the lowest levels of the brain stem as judged by the occurrence of opisthotonus and the attitudes of decerebrate rigidity. There was also evidence of overactivity in the autonomic nervous system; the dilation of the pupils, flushing of the face and rapid pulse as sympathetic overactivity, the contraction of the pupils and pallor as parasympathetic overactivity. It was extremely difficult to separate these rapidly changing pictures and fit them into neurological schemes. The general impression was that of an overactive, totally disorganized central nervous system being thrown into activity in a rhythmical manner. It suggested to me the term "neuro-physiologic crisis." All of the neurologic manifestations, in spite of their severity, were reversible in character and the patient awoke from his hypoglycemic coma with no trace of the "neurologic storm" through which he had passed. He then would ultimately quiet down and remain stuporous. After full awakening he would still show some evidence of mental confusion for many days and at times as long as two or three weeks. The doctors had made the interesting observation that patients who experienced this severe complication usually emerged from this confused afterstate with definite signs of progressive improvement.

It is at present difficult to understand what occurs during this hypoglycemic treatment and what sort of nervous involvement produces these neurological pictures. Speculation, in the present state of our knowledge, may be interesting but is quite valueless. A great deal of work must be done. We hope that future study and evaluation of the hypoglycemic therapy may disclose some information which might help us to explain these unusual neurologic states. Until then, we must be content with close observation and careful recording of data.

AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

MOTOR INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN PELLAGRA; A REPORT OF 2 CASES *

By M. A. BLANKENHORN, M.D., *Cincinnati, Ohio*

NERVOUS and mental symptoms are conspicuous in textbook descriptions of pellagra, but only the more extensive studies describe motor disturbances other than peripheral neuritis. Hemiplegias and paraplegias are described as being rare and generally occurring in the severe and terminal stages. Grinker [1] in a recent textbook states briefly that a picture similar to the neurological complications of pernicious anemia may appear but are never as severe or progressive. He states further that the lesions of the nervous system in pellagra are "not irreversible."

With newer methods of treatment, especially with new forms of diet and vitamin concentrates, the severe and so-called incurable phases of pellagra can be cured [2] and profound disturbances of the central nervous system reversed. The cases here presented, one resembling hemiplegia and the other diplegia, were totally disabled and even "helpless," one for three weeks and the other for six weeks. With intensive dietary treatment both became well. In each case chronic alcoholism was the obvious predisposing cause of pellagra, but it is now generally believed that "alcoholic pellagra" and endemic pellagra are the same disease. In 1928 Klauder and Winkelman [3] reported finding "central neuritis" in every case of pellagra which they examined histologically, a total of 11 cases, and in many cases of alcoholism in which a diagnosis of pellagra had not been made.

The remarkable recovery of the patients here described, when treated as pellagrins, suggests that the motor involvement was really part of the pellagra syndrome.

CASE REPORTS

Case 1. L. C., a 48 year old Negro laborer, was admitted to the Medical Service of the Cincinnati General Hospital April 18, 1936, complaining of "fits" of two days' duration. He gave a history of two similar attacks 10 years previously, and of alcoholism, up to one pint daily, for years. During the three months prior to admission he noticed loss of appetite, soreness in the chest and abdomen, slight loss of weight, and aching and weakness in the lower extremities. The day before admission he had two generalized convulsions which he could not adequately describe, even though he claimed he was conscious throughout the "fit."

Physical examination revealed a fairly well developed, fairly well nourished Negro

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who was restless, disoriented, confused, at times delirious, and who made purposeless choreiform movements of his arms and legs. His lower extremities were weak and he was unable to walk. The right pupil was irregular and larger than the left; both reacted only slightly to light. The skin and mucous membranes showed the diagnostic signs of pellagra. The margins of the tongue were smooth and red, and areas of leukoplakia were present beneath the lateral margins. The gums and oral mucous membranes were also red and beefy. The skin showed increased pigmentation, roughening and desquamation of the dorsum of the hands, and of the feet, elbows, and knees. The lesions of the hands were sharply demarcated from the healthy skin of the forearm. Examination of the central nervous system showed knee jerks which were thought to be normal. Ankle, abdominal, and cremasteric reflexes were absent. There was no ankle clonus or Babinski reflex. Sensory examination was impossible. Blood pressure 130 mm. of Hg systolic and 80 diastolic.

Laboratory Findings. Hemoglobin 80 per cent (Sahli); red blood cells 3.9 millions; white blood cells 14,000 with 82 per cent neutrophiles. Urine: Specific gravity 1.032 (later becoming normal); sugar and albumin 1 plus; many granular casts. Later examinations were negative. Blood Kahn test negative. Spinal fluid examination negative, except for positive protein on admission; later examinations were normal. Gastric analysis following Ewald meal: 24 per cent free HCl, 54 per cent total HCl. Blood sugar, blood urea-nitrogen, and carbon dioxide combining power were normal.

Progress. During the first two days of hospitalization the patient had 18 or 20 "convulsions," each consisting of clonic twitching of the extremities, usually of the lower extremities only, accompanied by opisthotonos, incontinence, and striking mental excitement. He was not unconscious during these attacks. For several days after admission he was delirious and uncoöperative. Incontinence of urine and feces persisted for six weeks after admission. He did not have diarrhea at any time during the course of his disease. Treatment with a high caloric, high vitamin diet, intramuscular liver extract and brewers' yeast induced definite and rapid improvement in the dermal lesions, tongue, and mental state of the patient. He continued, however, to show marked motor incoördination with a rigidity so great that he was unable to leave his bed or to feed himself. At times his picture suggested a left spastic hemiplegia. On May 11 (twenty-fourth hospital day), he was examined by Dr. H. D. Fabing of the Division of Neurology who found spasticity of the left arm with hyperactive reflexes, absent reflexes in both legs, fascicular twitching in all muscles, Oppenheim on right and Gordon on left. He made a diagnosis of "toxic encephalopathy with left sided focal signs." Dr. Fabing again saw the patient on June 3 (forty-fifth hospital day) and described slight left facial weakness, increased deep reflexes on the left, bilaterally absent ankle jerks, bilateral Gordon, Oppenheim on the right, groping movements of the hands, and speech containing jargon. His interpretation was "Diffuse encephalopathy (demyelinizing) with "pellagra," with a suggestion that there might be accompanying peripheral neuritis.

Rapid improvement continued and 11 weeks after admission, the patient was discharged. At that time he was mentally clear, and was able to walk about the ward rapidly and without help. However, he still complained of inability to use his legs as well as formerly and there was slight residual rigidity of the left arm. Eight months after discharge an investigator learned that he had gone South to his old home to look for work, supposedly well.

Case 2. T. C., a 28 year old negress, was admitted to the Psychiatric Service of the Cincinnati General Hospital May 12, 1936 in a state of mild delirium.

Present Illness. During the four years preceding admission, this patient had been consuming large amounts of strong alcoholic beverages. Her sister described two previous spells of extreme nervousness accompanied by visual hallucinations.

During the three months prior to admission, she had become progressively weaker and, because she was "unable to prepare her meals," had been eating a diet which her sister felt was deficient. Two days before admission she suddenly screamed and began to make purposeless movements and meaningless sounds. Soon afterwards she had visual hallucinations. This condition persisted until admission.

Physical examination showed a well developed but poorly nourished black female who was oriented only intermittently as to time and place. She refused to answer questions and made slow purposeless movements of her entire body, head and extremities, and picked at her clothing, breasts, vulva, and anus. At times she sat up in a bizarre manner. The skin showed diagnostic signs of pellagra,—namely, rough, desquamating dermal lesions were present over the hands, wrists, feet and ankles. The tongue and mucous membranes were normal. Reflexes were equal and active; no plantar reversal. Temperature 99.2° F.; pulse 96; respirations 20. Blood pressure 135 mm. of Hg systolic and 90 diastolic.

Laboratory Findings. Red blood cells 4.63 millions; hemoglobin 80 per cent; white blood cells 12,000. The urine was normal; the blood Kahn test strongly positive, and the spinal fluid negative. Gastric analysis showed no free hydrochloric acid before or after histamine.

Progress. For several days after admission the patient continued to be mentally disorganized, restless, and to have hallucinations and periods of intense fear and severe insomnia. These symptoms fluctuated considerably from day to day. She became unable to walk and was incontinent of urine and feces. Neurological examination revealed peripheral tenderness, great incoördination, and striking bilaterally symmetrical rigidity, especially of the legs. Through the courtesy of Dr. E. A. North of the Division of Psychiatry she was seen on her seventh day of hospitalization by the author who concurred in the diagnosis of pellagra. Treatment, which had been started on admission, consisted of a high caloric, high vitamin diet, dry powdered brewers' yeast, parenteral liver extract and moderate sedation. She improved rapidly and within three weeks she was able to feed herself and could walk moderately well, although spasticity of her legs persisted and she was still mentally confused. Despite the fact that she was known to be chronically addicted to alcohol, she was not classed by the psychiatrists as definitely of Korsakoff's syndrome and no opinion other than the diagnosis of pellagra and chronic alcoholism was offered as to the cause of the striking motor disturbances. On her twenty-seventh day of hospitalization (6–8–36) she was transferred to Longview Hospital for the Insane. Upon discharge from that institution 10 weeks later, she had no abnormal motor behavior, could walk rapidly with perfect coördination and was mentally clear. When seen one year later, this patient stated she was no longer drinking, she appeared to be in excellent health, and had had no return of symptoms since leaving the hospital.

Comment

Two adults who had motor involvement of the central nervous system at a time when they had diagnostic pellagrous lesions are presented in the present report. Both patients were addicted to alcohol. They had severe motor disturbances characterized by rigidity, inability to walk, and slow choreiform movements. The paralysis in one case was hemiplegic in type, while in the other it was paraplegic. Following the administration of a high caloric, high protein diet and large amounts of powdered brewers' yeast, the pellagrous dermatitis disappeared and the motor function of the central

nervous system was restored in both cases. The observations in this report show that motor involvement of the central nervous system, like glossitis and dermatitis, is part of the syndrome of pellagra and responds as do these symptoms to antipellagric therapy.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

NUTRITIONAL DISTURBANCES OF THE EXTREME SOUTH *

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KNOWING the life long interest that Dr. Pratt has had in dietetics, the keen enthusiasm he has shown on the subject of nutrition, and appreciating the magnificent dietetic facilities that he has organized in his clinic, it seems appropriate to present some observations on the nutritional disturbances that are observed in the far South.

There is considerable variation in the type of patients seen in the wards of a large general hospital in the South as contrasted with the wards of a Northern metropolis. In the North it is customary to see many cases of rheumatic heart disease, for example, but in the South these cases are relatively rare. True lobar pneumonia is an exception in the South and never are cases observed in large numbers at one time as they are in the late winter in northern climates. On the other hand, there are seen in the South patients who have sprue, who have pellagra, who have malaria, amebic dysentery, bacillary dysentery and other types of disease which are relatively infrequent in the North. Many of these disorders are representative of the so-called tropical diseases but actually diseases observed in the tropics, or the sub-tropics as is New Orleans climatically, are pretty much the same diseases that are seen in temperate climates. The difference is merely quantitative rather than qualitative. More cases are seen probably of sprue or pellagra in the South and fewer cases of pneumonia than in the North, but as many cases of hypertensive heart disease or of syphilis are seen in the tropics as are seen in the North. As brought out recently by Haines, sprue is very much more common in the North than it was thought to be at one time. Alcoholic pellagra is observed repeatedly in the North. At one time the population of Philadelphia was almost decimated by malaria. Amebic dysentery is ubiquitous. Leprosy is world wide in its spread. Really it might be said that, with the exception of certain dermatologic conditions, diseases of exclusively tropical distribution are almost non-existent.

Just as the so-called tropical diseases are more frequent in the South than in the North, likewise there is another group of cases which seem to be commoner in this southern section of the country than elsewhere. Perhaps this impression is erroneous and the apparent greater frequency of these disorders depends upon our searching for them more carefully and being more on the watch for them than in the past. These disorders are

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dependent upon some nutritional inadequacy. They exist as clear-cut, definite entities which depend upon such extrinsic causes as faulty diet or they may, on the other hand, be dependent upon some inherent defect in the organism as in pernicious anemia. The clear-cut syndromes may develop as result of vitamin insufficiency, inadequate and improper mineral intake or a lack of protein. It is my purpose to illustrate succinctly the expressions of some of the clear-cut definite entities and how they can be handled and then to discuss rather briefly the indefinite ill health which may be associated with nutritional faults which do not produce actual nosologic entities.

Pellagra

In Louisiana the incidence of pellagra waxes and wanes but on the whole it seems to be less common than it was a few years ago. It is surprising how severely ill some of the patients are who come into the Charity Hospital suffering from pellagra. It is also astonishing how these people sometimes fail to respond to what is now considered to be more or less a standardized treatment. Illustrating this is the case of Mrs. A. who was brought into the hospital June 1937 with a severe diarrhea. She had been confined to bed for some weeks; she showed very little dermatologic reaction; her mentality was distinctly obtunded. This woman was markedly undernourished, dehydrated, with extremely sore mouth and with a proctitis and extremely severe vaginitis. She was given fluids by vein, a high caloric-protein diet largely liquid on account of the stomatitis, powdered brewers' yeast, vitamin concentrates and even liver extract hypodermatically. In a few days improvement of the mouth and of the mental state was quite decided. The proctitis and vaginitis showed no signs of improvement. The diarrhea was controlled. In spite of temporary improvement the patient relapsed and died a few days later. This patient had in her diet an over abundance of the important elements, the lack of which may play a part in the production of pellagra. In spite of this, death occurred rather promptly. It is most discouraging in patients of this type to carry out the indicated lines of therapy and to get no result, but these cases are quite common. Incidentally it might be noted that the so-called alcoholic pellagra is rather uncommon in our wards.

Pernicious Anemia

The most remarkable feature of pernicious anemia that I have observed in a woman's ward is the extreme degree of anemia these people have when they come into the hospital. It is perfectly astounding. A large number of these patients are seen. Illustrating the statement as to the severity of the anemia, is the case of Mrs. B. who entered the hospital on account of weakness, loss of weight and loss of appetite. This woman had been sick about six months. On admission to the ward she had a red cell count of about 1,000,000, hemoglobin 3.67 grams, mean corpuscular volume of 134

cu. mm. but no absence of free HCl. Parenteral administration of liver extract brought about a sharp reticulocyte response and improvement took place very rapidly. When discharged from the hospital in about a month the blood count had reached practically normal figures, mean corpuscular volume approached normal and in every way the patient was to all intents and purposes entirely well.

Unfortunately on account of lack of financial resources and because many of these patients live in country districts where the free clinic is not available, they leave the hospital in excellent shape and return again in a period of about six months to a year or two almost as anemic as they were when they first entered. We can build them up again, out they go and then sooner or later they return. I had one patient who has been in the hospital seven different times, admitted each time with a high degree of anemia and each time she goes out in excellent condition.

Unlike pellagra, pernicious anemia is a most satisfactory disease to treat. Since the introduction of liver extract I have not observed a single death of a patient from this disease.

Sprue

In a hospital ward of 21 beds which are always filled, probably four or five cases of sprue can be expected during the year. One of the cases that I have observed was that of Mrs. S. who went into the hospital with severe diarrhea, stomatitis and an extreme degree of emaciation, weighing 59 pounds. I am recounting this case because I have kept in constant touch with her for nearly eight years and she is apparently well. Mrs. S. was placed upon a diet consisting largely of bananas and raw pancreas. After many days of encouragement to get her to follow this regime she was finally able to eat about two or three dozen bananas a day; her improvement began at this time. After a period of six months she had more than doubled her weight. The diarrhea disappeared and the anemia had gone. She now retains a weight of 130 to 135 pounds and has continued to eat bananas to the extent of three or four a day. From time to time she has slight diarrhea and as soon as this develops she takes a dozen or two dozen bananas and restricts her diet almost entirely to this article of food. In a day or two the diarrhea will have gone and she is back again to normal health. This patient never had liver extract. Nowadays we are including with the banana diet injections of liver.

Sprue was at one time thought to be solely a tropical disease but Haines calls attention to the relative frequency of sprue in North Carolina, and Snell records nine cases appearing at the Mayo Clinic in one year. Undoubtedly sprue has been often misdiagnosed as pernicious anemia. It is important to make the correct diagnosis because, as Haines writes, these patients with sprue can be cured if the proper diagnosis is made and if proper treatment is instituted they will not have to go through life living on liver.

Scurvy

Once in a while I see obvious cases of scurvy but they are relatively rare. On the other hand, subclinical scurvy is by no means uncommon. A young pregnant woman was admitted to my ward with petechiae and a story of having had hemorrhages, small in amount, from the mouth and from the rectum. The blood studies were entirely negative. Although she had been taking vitamin C to a limited extent she, as every pregnant woman, required a superabundance of vitamin C which she had not been getting. The purpura cleared up and there was no further hemorrhage after giving her large quantities of orange and tomato juice.

Beriberi

In a group of Louisianans who are poverty stricken the diet consists largely of red beans and rice. These people often develop beriberi. Such patients are seen from time to time so that we are always on the watch for it and are not surprised when these cases appear. A young person came into the hospital with an atrocious mouth, Vincent's angina. Several weeks prior to the development of the mouth condition there was marked weakness of the legs and some anemia. The condition became very much exaggerated when the patient was unable to eat on account of his sore mouth. Upon historical and physical examination the typical symptoms and signs of mixed beriberi were found to be present. After curing the mouth condition, the institution of a diet which contained vitamin B to excess promptly relieved the symptoms. From time to time I have seen patients who have recurrent attacks of beriberi. It may be noted that improvement is prompt and satisfactory after the first or second attack. The subsequent attacks fail to respond to treatment and the patient may be left permanently crippled.

Protein Deficiency

Quite commonly there is observed among our clientele patients who have voluntarily, or through poverty, restricted their protein intake to a point where anemia develops and even edema ensues. These people do not have edema as a result of depletion of plasma proteins through a nephritis or a nephrosis, but merely as a result of insufficient intake. Probably the most outstanding case was that of a young woman who had been advised by her physician, on account of a gall-bladder disorder, to withhold proteins. Conscientious and faithful in observance of the doctor's orders, this woman for a period of six months stopped eating every type of protein. When she was first seen she had marked edema of the legs, so marked as a matter of fact that she had some difficulty in getting about. There was complete reversal of the serum albumin-globulin ratio and serum albumin was well below edema levels. She was given a dozen eggs in the course of the next 12 hours and the diuretic effect was astounding. Edema quickly disap-

peared and since then she has had no further trouble. As in every general hospital a certain proportion of the people are admitted on account of extreme inanition. It is not uncommon to find these people with varying degrees of edema which disappears when they are given a well rounded diet.

Chronic Dietary Deficiency

Excluded from this group are those patients whose diet contains ample energy requirements, likewise those people who have some distinct and definite disease which may account for an excessive expenditure of energy, such as exophthalmic goiter, or who lose ingested food through the alimentary tract as the result of diarrhea. The patients of the group, to which I am referring, are not, strictly speaking, undernourished, but their body weight is subnormal and they have a variety of symptoms which may be attributed to an illy balanced diet. To those symptoms Sodeman and I have applied the term chronic dietary deficiency. These patients do not present clinical entities which have a nosologic significance. Possibly many of the cases might be called subclinical forms of diseases such as beriberi or scurvy or what not. Rather than mentioning specific instances which are extremely common in our section of the country, it may be more appropriate to run over briefly some of the expressions of this type of disorder. These people are usually thin, and anemia is a constant concomitant. We have seen patients who have macrocytic anemias yet do not have pernicious anemia, but more common is microcytic anemia. Some of the signs and symptoms that they present may be due to vitamin A deficiency, such as photophobia and dry skin. Gastrointestinal symptoms are common with dyspepsia, anorexia, constipation. There may be nervousness, headache and irritability. In younger individuals growth is impaired, dental caries may be observed and gingivitis with bleeding is common. They often have susceptibility to infection and vague aches and pains. They have ease of fatigue and weakness. Paresthesia and tingling of the extremities are by no means uncommon. These patients may have the features of the neurotic and the complaints of the neurotic. An analysis of the diet of these patients with chronic dietary deficiency, and a complete dietary history will show that they restrict the protein, fruits and fresh vegetables in their diet, through poverty or idiosyncrasy. Butter fat may disagree with them and they often eliminate that from the diet. Frequently their main article of food is carbohydrate. They live on what I have termed a "white diet." If these individuals, usually for economic reasons unable to pay for a well rounded diet, can be given a liberal supply of fish, meat, eggs and cheese, irradiated evaporated milk, fruits, tomato juice and cod liver oil, their improvement is sometimes astounding and the disappearance of the so-called neurotic symptoms is almost miraculous. Strange to say, chronic dietary deficiency is rarely observed in the negro, although they are the poorest section of our population. However, to the negro food is the first thought in his mind

when it comes to spending his wages, whereas other considerations such as where and how he lives, how he clothes himself and so on are entirely secondary.

Conclusions

No attempt has been made to detail systematically the nutritional disorders that are observed in the South. The more common ones have been discussed in a general and rather informal way. These disorders are extremely common and are most satisfactory to treat, with this proviso, and it is a big one, that funds be available to supply the patient with the proper foods.

AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DR. JOSEPH HERSEY PRATT

COFFEE AS A CAUSE OF CARDIAC PAIN *

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THERE are many disturbances, both anatomical and physiological, which may cause pain in the region of the heart. To differentiate them and, in a given case, to determine the particular condition giving rise to discomfort, is the first requisite in diagnosis. The accurate definition of etiology often makes possible the distinction between a mild and a grave malady; it is essential for the institution of effective therapy.

As a cause of cardiac pain the drinking of coffee has received but scant attention, though briefly mentioned by some of the older clinicians. For example, Krehl [1] states that "poisoning by coffee may cause more complete systole of the ventricles, palpitation, oppression and anginoid states." He ascribes these effects to two causes: first, to direct stimulation of the heart; and second, to more forceful contractions which represent a compensatory reaction to peripheral vasoconstriction. Allbutt [2] remarks that "coffee drinkers, and some nervous persons are liable, especially in later life, to attacks of cardiac irregularity, especially during and after meals, with epigastric distention, oppression, or even pain, a series which, with some degree of arteriosclerosis in radial artery and aorta, may simulate *epigastric angina* very closely." In the latest edition of his manual of pharmacology, Sollmann,[3] in discussing the toxicology of caffeine, says: "With larger doses, the pulse is full and hard, quickened or slowed, with palpitation and precordial distress (sometimes anginal attacks)." In a recent monograph I have made brief reference to the cardiac pain due to coffee [4]; but most of the newer texts on diseases of the heart fail to mention it, although a number of other toxic effects are noted, particularly premature contractions. In the following two cases, the relationship between the drinking of coffee and the occurrence of pain seemed clearly established.

CASE REPORTS

Case 1. A physician, aged 38 years, was first seen in December 1927. He complained of precordial pain of two months' duration. He had enjoyed excellent general health. He played squash two or three times a week without discomfort. He was working hard and nervously awaiting the birth of a second child. Up to three weeks before his visit, he smoked six or eight pipefuls each day. He rarely took alcohol. He drank two large cups of coffee and two cups of tea daily.

The present illness began two months previously, with an arrhythmia due to premature beats. He stopped smoking on this account. For four weeks he had

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noted pain in the chest, usually precordial, but sometimes substernal. This was not severe, was unrelated to effort and lasted for several hours or even for several days. There was sometimes a sense of heaviness in the left arm. He played squash without aggravating the discomfort. There was no dyspnea. He was much upset because of the possibility that his symptoms indicated the presence of coronary sclerosis.

On examination there were so signs of organic cardiac disease. The heart rate was 60; the rhythm regular. The sounds were normal. The blood pressure was 118 mm. Hg systolic; 72 diastolic. The heart was transverse in position, but was not enlarged on roentgen-ray examination. The electrocardiogram showed a moderate degree of left axis deviation, with inversion of the T-wave in Lead III.

He was reassured and advised to stop taking coffee and tea. He was told to resume smoking in moderation and to continue with his usual exercise.

One month later he reported that the pain in the chest had completely disappeared and that a cup of coffee or tea would bring it on as before. Even Sanka induced discomfort. Because he was still somewhat skeptical as to the relationship of coffee to his pain, the following experiment was carried out: At intervals of a week, for four consecutive weeks, he was sent a capsule, the contents of which were not known to him. Two of the capsules contained 0.13 gm. (2 grs.) of citrated caffeine, the others an equivalent amount of milk sugar. He was able to distinguish between them in each instance; the caffeine precisely reproduced the pain which he had been having; the milk sugar caused no symptoms.

He was seen again seven months after his first visit. He had attempted to take coffee, but found that it again caused pain. Examination was negative, as before.

In November 1932, the patient reported that his sensitiveness to coffee had disappeared and that he could now drink it without subsequent pain.

In March 1937, he reported that he had been drinking coffee during the intervening years without recurrence of cardiac pain. At times, however, about an hour after taking a cup of coffee there was marked sweating of the palms of the hands. He was convinced that coffee caused his original symptoms.

Case 2. A lawyer, aged 40 years, was first seen in December 1930, complaining of precordial pain which had been present, at intervals, for a year. At 18, he had nephritis and was out of school for a year. Subsequent tests of renal function showed a good recovery. He was refused for military service in 1918, because of albuminuria. There had never been hypertension or edema. He took two cups of coffee each day, but no tea. He did not smoke or use alcohol. He was of a worrisome nature and dreaded trial work, which, because of the limited business available, he was obliged to undertake. He had been married 12 years; his wife and two children were living and healthy.

The present illness began the year previously. He was in the habit of playing squash several times a week. Always, after exercise, he noted upper precordial pain, not severe and without radiation. This would usually last for several hours; "it felt as though a muscle had been pulled." There was a tender spot in the region of the third left interspace. The pain never occurred during exercise, but always after it. He could walk briskly for two or three miles, but on sitting down later would have an aching sensation in the precordium for two or three hours. There was no dyspnea. He consulted a physician, who suggested that an electrocardiogram be taken by a diagnostic laboratory. The report stated that the myocardium was severely damaged. He was advised to give up all exercise and to curtail his work. He was naturally greatly distressed.

The patient was a high-strung, introspective man. Physical examination was negative. There was no evidence of arterial or arteriolar sclerosis. The heart rate was 80; the rhythm regular. The sounds were of good quality. The blood pressure was 146 mm. Hg systolic; 86 diastolic. There was no enlargement of the heart by orthodiagraphic measurement. The electrocardiogram showed slight notching of the

S-wave in Leads I and II, and of R in Lead III. There was also very slight elevation of the S–T segment in Leads II and III (figure 1). The urine contained a faint trace of albumin, but no casts or blood cells.

The patient was told to resume a normal life, including the playing of squash. He was advised to give up coffee.

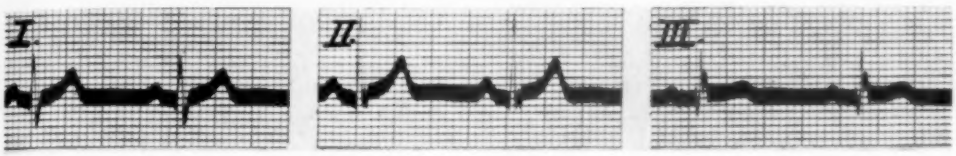

FIG. 1. Electrocardiogram of Case 2. For description, see case report in text.

Two months later, he stated that he had an occasional twinge of pain after violent exercise, but this was negligible. He was still working under strain. The blood pressure was 136 mm. Hg systolic; 84 diastolic. In April 1934 (four and one-half years after his first visit) he stated that he had never been so well. The cardiac pain had completely disappeared. He was playing squash and working hard.

He was seen again in June 1935. He was much happier and had been very successful as a lawyer. He had given up squash, but played doubles at tennis and walked briskly without discomfort. He again wanted an appraisal of his condition. Examination was essentially as previously described. The electrocardiogram was exactly as it had been on the first examination.

The patient reported by telephone on July 9, 1937. His general health was excellent. There was no recurrence of pain and he felt certain that his original discomfort was due to coffee. He drank Sanka or Kaffee Hag, but had not tried coffee. He continued to play tennis and golf. He was effusive in his gratitude and felt that by giving up the use of coffee and being reassured about his heart, he had been spared a life of invalidism.

COMMENT

These two cases are examples of a small series seen in office practice. They are particularly significant because of the relatively long follow-up periods, namely nine and one-half years in one patient, six and one-half in the other. The experiment with caffeine carried out in the case of the physician demonstrated conclusively that, in this instance, discomfort was due to the caffeine content of the coffee, not to reflex digestive disturbances induced by its volatile, oily constituents. The slight changes in the form of the electrocardiogram in the second case served at first to confuse the clinical picture but proved to be a source of unnecessary concern.

The number of such cases is not large; but, in my experience, cardiac pain due to coffee is more common than that due to tobacco.[4] Tea, because it is taken weaker and, as a rule, in smaller quantities, is less frequently concerned. This type of pain occurs predominantly in persons with apparently normal hearts; discomfort caused by tobacco is more frequent in patients with diseased coronary arteries who have already experienced spontaneous attacks.

The character of the pain is different from that of the so-called

"anginal" type, in that it is not severe, is of relatively long duration and is not induced by effort or emotion. It may radiate to one or both arms, causing a sensation of heaviness or soreness. When present, it is not aggravated by exercise. The discomfort is not relieved by taking nitroglycerine. Physical examination reveals no signs of organic cardiac disease. In spite of these distinguishing features, mistaken diagnoses have been made and patients have been alarmed and restricted in their activities without good cause.

All of those whom I have seen with pain due to coffee have been high-strung, tense individuals. Several have been under mental and emotional stress, induced by such causes as economic difficulties, marital incompatibility or a heavy load of responsibility. The question may be asked as to whether they were suffering from a psychoneurotic state with cardiac symptoms. This seems unlikely, for the pain disappeared promptly after stopping the use of coffee in each instance. It is more probable that their increased susceptibility to coffee was due, in part, at least, to a lowered nervous threshold. The subsequent history of the physician (Case 1) indicates that this susceptibility may be transitory. The course of these patients has shown that they were not suffering from any serious, organic cardiac disease; coronary sclerosis, if present, has not manifested itself by symptoms or signs. The lawyer (Case 2) has so far enjoyed almost 10 years of active life and has achieved, during this period, conspicuous success in his profession.

The action of caffeine on the heart and blood vessels is both central and peripheral, varying with the amount taken. A cup of coffee or strong tea contains about 0.1 gm. (1½ grs.) of the alkaloid. The predominant action of moderate doses consists in vasodilation combined with cardiac stimulation. The heart rate is accelerated, the amplitude of cardiac contractions is increased and cardiac output is correspondingly augmented. In experimental animals, the coronary blood flow is increased. The areas of the brain which control psychic processes and the medullary centers (respiratory, vasomotor, vagus) are stimulated.

The usual effects of poisoning due to coffee are nervousness, palpitation, insomnia, headache and digestive disturbances. In susceptible persons, especially those of "nervous" disposition, these symptoms are exaggerated. Chronic caffeine poisoning causes palpitation which is sometimes associated with a cardiac arrhythmia, most frequently due to premature beats. Dyspnea may occur. Neuralgias of various sorts have also been described.[5]

Brow, Long and Beattie[6] injected caffeine intravenously into decerebrated cats and produced extrasystoles. This result was obtained after all nerve connections to the heart were severed and the suprarenal glands were removed. They concluded that the site of action of caffeine was either on the myocardium or the sympathetic nerve endings in the heart. Dikshit,[7] on the other hand, observed that caffeine could produce extrasystoles by an action on the hypothalamic centers.

It appears, then, that caffeine may affect the heart both by its direct effect on the cardiac muscle and nerves, and indirectly through the hypothalamus. The manner in which it causes cardiac pain cannot be explained satisfactorily until more definite information is at hand concerning the mechanisms by which painful stimuli are initiated in the heart. The fact remains that, in certain persons unduly susceptible to caffeine because of increased nervous irritability or for some other unknown reason, coffee may induce cardiac pain. To recognize the existence of this relationship is, on occasion, of practical clinical importance.

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CASE REPORTS

MYXEDEMA AND DIABETES MELLITUS: A CASE REPORT WITH AUTOPSY FINDINGS *

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The patient reported in 1930 [1] as having the rare combination of myxedema and diabetes died in November 1936 of carcinoma of the bowel. An autopsy was done and the complete report of the case is herewith presented (summarized in table 2).

The number of cases in the literature is not large. Shepardson and Wever [9] and Weinstein [10] have recently added to the series and in so doing have sufficiently surveyed the literature and the subject in general. One additional case (Castex et al.) has been reported since their article appeared and a summary of the total series is given in table 1. The autopsy record herewith reported on our case is the second one in the literature, the other being that of a case of Weinstein's.

Table I

Cases of Spontaneous Myxedema and Diabetes Mellitus

Ewald	1895	Berl. klin. Wchnschr., 1895, xxxii, 25.
†Gordon	1904 (2)	Am. Med., 1904, vii, 299.
Shasser	1905	Jr. Am. Med. Assoc., 1905, xliv, 765.
†Holst	1923	Schweiz. med. Wchnschr., 1923, iv, 725.
Brown	1924	Lancet, 1924, i, 59.
†Wright	1926 (2)	Clifton Med. Bull., 1926, xii, 88.
Wilder	1926	Arch. Int. Med., 1926, xxxviii, 736.
Jamieson	1927	Canad. Med. Assoc. Jr., 1927, xvii, 88.
Carey	1930 (1)	Minn. Med., 1930, xiii, 578.
Carey	1926	Same case with autopsy herewith reported.
Weinstein	1932 (2)	One autopsy—Johns Hopkins Hosp. Bull., 1932, li, 27.
Daniels	1932	Nederl. tijdschr. v. Geneesk., 1932, lxxvi, 1555.
†Joslin	1928 (3)	The treatment of diabetes mellitus, Lea and Febiger, 1928, p. 890.
Joslin	1933	Quoted by Shepardson and Wever.
Shepardson and Wever	1933	Internat. Clin., 1934, iv, 132.
†Rohdenberg	1922	One case with autopsy, Endocrinology, 1922, vi, 519.
Castex, M. R., Scheingart. M., Mollard H.	1933	Rev. Sud. Am. de Med. et de Chir., 1933 iv 1.

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† The cases reported by Gordon, Holst, Wright, Rohdenberg and one of Joslin's in 1928 are open to some question; that of Holst for instance was postoperative myxedema, not spontaneous; Gordon's cases were not well studied as to basal metabolic rate; and Wright's cases may have been only hypothyroid, although they seemed to have some of the symptoms of myxedema. One of Joslin's cases is of this same character, and in Rohdenberg's case the "diabetes" had disappeared before the onset of the myxedema. An autopsy done in this latter case showed atrophy of thyroid and hypertrophy of islands of Langerhans of the pancreas, but detailed studies of neither metabolic conditions were made during life.

TABLE II

Date	Basal Metabolic Rate Per Cent	Weight Kg.	Blood Sugar Per Cent	24-hour Urine Sugar Grams	Thyroid Substance Per Day Grains	Units Insulin Per Day	Diet
6–29–21	−36	75.8	—	—	6	—	This diet continued all
10– 3–21	− 6	66.0	—	—	4–6	—	during this period as well as
4– 3–22	+ 2	76.4	—	—	4–6	—	his wife could manage it.
8–28–28	−17	70.0	.174	—	4	15	It certainly was not accu-
9– 1–28	—	—	—	33	2	30	rately maintained.
9–14–28	+27	66.0	—	4	2	30	Carbohydrate 110
10– 5–28	—	—	—	3	2	30	Protein 70
10–18–28	+ 7	69.0	—	—	2	30	Fat 180
12–20–28	+12	67.0	—	13	2	30	
7–17–29	+ 1	58.0	.285	—	2	30	
3–31–30	+11	60.0	.222	—	2	30	
4– 4–30	—	—	—	8	2	35	
11–14–30	+ 2	60.0	.384	10.5	2	45	
12– 3–30	—	—	—	reduction	2	40	
12–18–30	—	—	—	none	0	36	
1– 8–31	—	—	—	none	0	30	
1–17–31	—	—	—	+qualitative	2	28	
2–16–31	—	—	—	+qualitative	2	31	
2–19–31	+ 6	60.0	.384	22.8	2	31	
3– 7–31	—	—	—	4.2	1	36	
9–11–31	—	—	.444	31.2	1	36	
12– 2–31	+ 3	73.0	.377	8.2	1	33	
4–14–32	—	74.0	—	2.4	½	33	
5–17–33	− 1	75.0	.449	—	1	36	
1– 5–34	+ 2	69.0	.654	28.2	1	57	

CASE REPORT

A. W. S., male, aged 44 years, appeared for examination June 28, 1921, complaining of weakness, aching legs and shortness of breath. He stated that in March 1920 he began to feel general malaise, was easily fatigued and had some aching of legs and dyspnea on exertion. He had been treated for pyorrhea at that time without relief of symptoms. Upon questioning, it was brought out that he had suffered from impairment of visual acuity; his mental processes were considerably retarded; and his hearing especially had become quite poor. He found it almost impossible to keep awake and would usually fall asleep anywhere if he remained in a sitting position for any length of time. He had gradually gained in weight and his flesh had become soft. He had become stooped and "round shouldered" during the past year and had experienced great difficulty in holding his head erect. His hair had become dry and had fallen out; his skin was dry, although he perspired readily. There had been some swelling of the legs from the knees down, which did not vary greatly on change of posture. His wife further stated that his pulse had become slow, being about 50 when she had counted it. The family and past history were unimportant. He had two children and his wife had had two miscarriages, both at about six weeks.

Examination revealed a dry, scaling skin, thin dry hair and scaly scalp. The face was puffy especially around the eyes, and the color was rather pale. General musculature was flabby with an increase of fat deposit at the back of the neck and on the abdomen. The pulse was slow (50 to 56), full in volume but of low tension. Respiration was also slow. As the individual was questioned, his attention wandered; his speech was slow and thick and his answers were often inaccurate when checked

by his wife. The eyes were negative except for a drooping of the upper lids. The examination as to heart, lungs and abdomen was entirely negative. The reflexes in the extremities were sluggish. There was no true edema but a typical myxedematous palpatory sensation of the subcutaneous tissue was present. The first blood pressure reading was 108 systolic and 80 diastolic. Important laboratory findings at this original examination were: Negative urine tests, a negative blood Wassermann and a basal metabolic rate of minus 36 per cent. He was placed on 6 gr. of desiccated thyroid substance daily and his subsequent course can be readily seen by reference to table 2. There was the expected symptomatic improvement and from 1922 to 1928 he was not seen, although we corresponded with him at intervals.

During the winter of 1927 he developed symptoms of diabetes; that is, he lost weight rapidly, had great hunger, thirst and weakness. The doctor in the town to which he had moved found sugar in his urine. There was great difficulty in establishing a proper balance between diet, glycosuria and thyroid dosage. Finally in August of 1928 he returned to the clinic for examination and management. At this time he was found to be thinner than before and without any signs or symptoms which one could identify as being myxedematous except that his pulse rate was slow and his basal metabolic rate was minus 17 per cent. The blood pressure at this time was 120 systolic and 80 diastolic. Again his course can best be followed by reference to table 2.

The patient was not very coöperative, insisting upon an adequate daily food intake in order to do his work as janitor. He would not report at regular intervals for checking up but usually came when either he or his wife was worried about something.

We tried to eliminate the thyroid substance, thinking that perhaps the diabetes might be better controlled if we allowed the basal metabolic rate to drop to 10 or 15 below normal. The patient, however, had a great fear of relapsing into his previous lethargic state and insisted upon taking a small daily dose of thyroid substance. During the time when he was first found to have diabetes he had a few unfortunate insulin reactions and had developed some fear of an over-dosage of it. Perhaps due to the peculiar combination of things in this case these personal factors are not very important, but they are recorded as a possible explanation for the difficulty in controlling the diabetic factor. If the basal metabolic rate had been allowed to drop below normal, and if the patient would have consented to either limiting his food intake or increasing his insulin dosage, perhaps the balance could have been better maintained.

He was, however, checked at intervals with results recorded upon the accompanying chart. It will be noted that his weight fluctuated slightly, and that his fasting blood sugar tended to remain at a higher level from 1930 on. The insulin dosage was varied from time to time by his wife, according to her ideas of his needs based upon an occasional examination of urine with Benedict's solution and the occurrence of mild insulin reactions. He complained frequently of cramping pain in his legs. His blood pressure on March 31, 1930, was 132 systolic and 78 diastolic and an electrocardiogram was normal in all leads (figure 1).

In September 1931 he suffered from an infection of the leg resulting from a varicose ulcer. During this time his wife reported the occurrence of much more sugar in the urine, so instead of modifying his diabetic program she eliminated the thyroid entirely until the infection healed—a period of about six weeks.

In December 1933 he became careless with his diet and his attending physician had to rescue him from an impending coma by the use of 200 units of insulin over a 24-hour period. Shortly after this he came to the clinic for examination, which resulted in the data noted under date of January 5, 1934 (table 2). In addition to these findings his sugar and insulin tolerance were studied by making blood sugar deter-

minations throughout the day on his regular routine. The results of this study were as follows:

9:30 a.m.	Fasting blood sugar 654 mg. per cent.
	20 units insulin administered and breakfast of approximately 24 gm. protein, 47 gm. fat and 78 gm. carbohydrates.
11:00 a.m.	Blood sugar 562 mg. per cent.
11:30 a.m.	Blood sugar 526 mg. per cent.
12:30 a.m.	Blood sugar 421 mg. per cent.
	20 units of insulin administered and lunch of approximately 26 gm. protein, 42 gm. fat and 18 gm. carbohydrates.
3:00 p.m.	Blood sugar 171 mg. per cent.
4:30 p.m.	Blood sugar 75 mg. per cent.
	At this reading a feeling of weakness, some sweating and slight tremor were noted, so he ate his supper early and returned home.

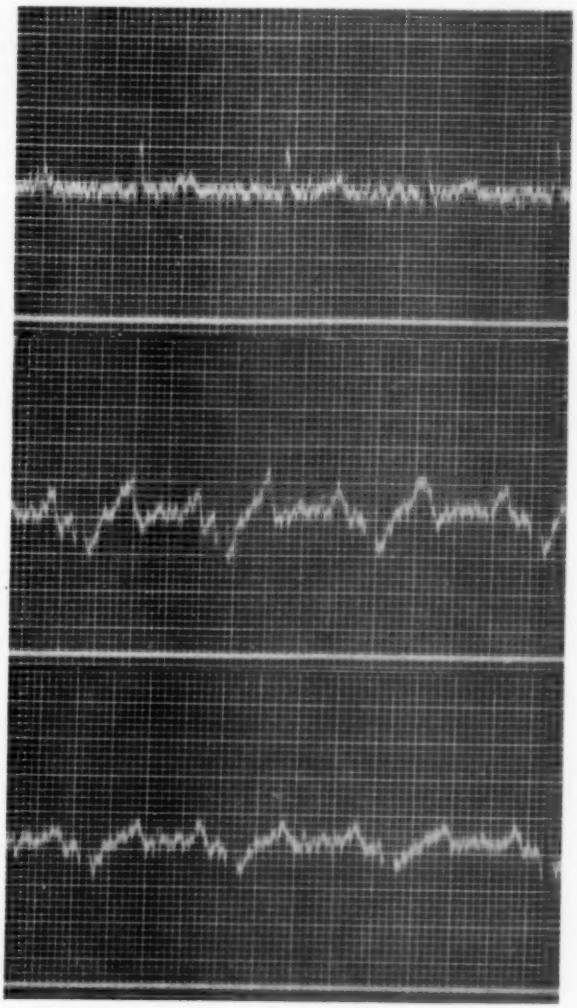

FIG. 1. Normal electrocardiogram (see text).

He was advised to discontinue his daily grain of thyroid, to adhere more strictly to his diet (which he still insisted must be adequate and which was of the approximate values shown on the chart), and to use insulin units 40–10–5 daily.

On July 22, 1935, he was brought into the hospital with a greatly distended abdomen. His bowels had not moved for several days and intestinal obstruction was suspected. His urine showed four plus sugar, acetone and diacetic acid. His breath was acidotic and his blood sugar was 770 mg. per cent. He was given 140 units of insulin with glucose together with colon irrigation, and over a period of 48 hours his acidosis cleared up and his urine became sugar free and also the supposed bowel obstruction was apparently relieved. At least the enemata brought away large amounts of fecal material and gas and the abdominal distention decreased. Previous to this he had been using about 45 units of insulin daily. He was discharged from the hospital without further bowel study and returned to his former program of diet, insulin and thyroid daily. His attending physician reported that from that time until the final events he had several attacks of abdominal distention relieved by enemata. After each such incident, however, his abdomen remained somewhat more distended than before. His bowels were usually constipated but with occasional attacks of diarrhea. The most violent of these attacks were in February and July 1936 and these were accompanied by coma. There was no vomiting at any time and very little pain. Finally about November 10, 1936, he showed signs of obstruction with enormous abdominal distention, this time not relieved by enemata or abdominal stupes. He became progressively weaker and finally died November 16, 1936. The autopsy was performed within five hours of death by Dr. E. H. Norris, whose record of the autopsy is as follows:

"The body is that of a well-developed white man, 185 cm. long, weighing about 170 lbs. The face, shoulders, arms, forearms and hands are extremely emaciated. The veins of the arms and shoulder regions stand out prominently. There is huge distention of the abdomen, the highest point above the table being 38 cm. There is marked edema of the lower extremities below Poupart's ligaments, a bit more marked on the left than on the right. There is tremendous edema of the scrotum and penis. Rigor is not present. Hypostasis is evident over the posterior parts; no cyanosis or jaundice. The pupils are 6 mm. in diameter.

"Upon incising the skin of the abdomen the edges retract spontaneously so that they are separated by a distance of 15 cm. before the peritoneum was incised. The peritoneal cavity contains about 500 c.c. of clear straw-colored fluid. The diaphragm reaches the third interspace on the right, the fourth rib on the left. The colon is hugely dilated from a point about 30 cm. proximal to the anus, where a firm small annular carcinoma apparently occludes the bowel. The dilated portion of the colon measures 42 cm. in circumference; the entire length of the colon, including the portion distal to the carcinoma, is 200 cm. There is moderate edema and slight dilatation of the lowest portion of the ileum. A large Meckel's diverticulum is present. The appendix is atrophic and presents as a white cord.

"The left pleural cavity has no adhesions, contains 200 c.c. of clear fluid. The right cavity is obliterated by firm adhesions. The pericardial sac contains about 40 c.c. of clear fluid and no adhesions.

"The heart weighs 250 grams. There is one white soldier spot on the left ventricle. There is no lesion on the valvular or mural endocardium. The musculature is of normal consistence, brown in color and shows no gross fibrosis. The coronary vessels are patent at their orifices; along their trunks they show grade I atherosclerosis with some thickening and slight narrowing of the lumena.

"The right lung weighs 400 grams, the left 220 grams. There is crepitation throughout both lungs but slightly diminished in both. The cut surfaces yield almost no fluid and no pus. The lungs appear drier than normal.

"The spleen weighs 75 grams. Its capsule is wrinkled. The pulp appears

fibrous and a number of small white nodules are scattered through it. The nodules vary from 2 to 6 mm. in diameter.

"The liver weighs 1300 grams. The capsule is smooth. Two areas of infiltrating tumor are seen through the capsule. On section several other white areas of infiltration are noted. These metastatic lesions are not large or extensive; the largest is about 5 cm. in diameter. The parenchyma of the liver is lighter in color than normal. A yellow cast is apparent and the general tone might be described as dark tan. The lobular markings are not clearly recognizable. The gall-bladder is markedly distended with thin dark bile; no concretions.

"The stomach, duodenum and small intestine are essentially normal, except as noted above. There is a small firm polypoid nodule projecting from the surface of the stomach about 1 cm. proximal to the pyloric ring.

"The pancreas weighs 55 grams. It is small and atrophic; the atrophy seems to be general but perhaps is most marked in the head portion. Microscopically the acinous and islet tissues appear normal morphologically. There is no increase in the fibrous stroma. The impression is strong, however, that there may be fewer islands in the tail region of the gland than is normal. The right adrenal weighs 6 grams, the left 6.5 grams. They appear normal.

"The right kidney weighs 130 grams, the left 160 grams. The capsules strip with ease, leaving smooth surfaces. The cut surfaces show no lesions. There is moderate dilatation of the right ureter, extending from the bladder to the region of the pelvic brim. The bladder shows no gross lesion. The prostate is small. The seminal vesicles, epididymides and testes show no gross lesions.

"The root of the aorta and the thoracic and abdominal portions show grade I atherosclerosis. A number of raised oval plaques are noted but there is no ulceration and no evident calcification.

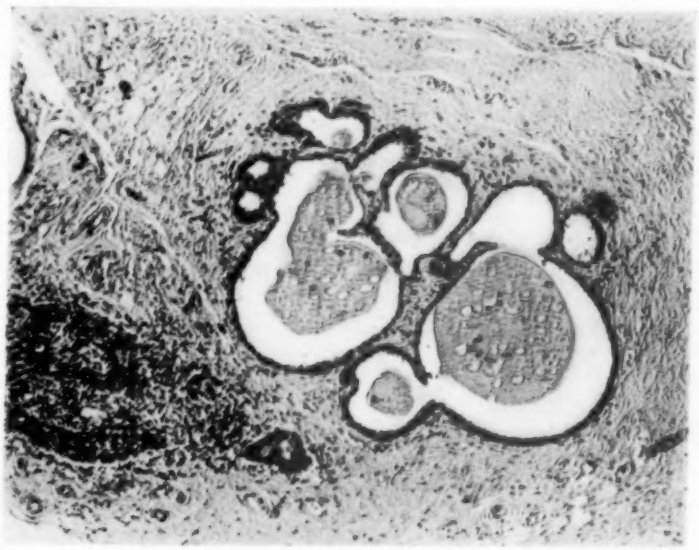

FIG. 2. Microscopic section of thyroid gland. (See text for description.)

"The organs of the neck are studied after removal of the larynx. The thyroid gland is scarcely recognizable; no normal thyroid tissue is apparent. The organ can be identified by the form and distribution of such tissue as is present, which is yel-

lowish white, very soft and flabby. Both lateral lobes, the isthmus and the pyramidal lobe can be recognized after careful dissection. The microscopic findings of the sections of the thyroid gland tissue showed almost complete replacement of the follicular parenchyma by collagenous fibrous tissue. In a few scattered areas greatly distorted epithelial structures can be found. (Figure 2.) Four parathyroids are recovered and appear to be normal.

"The lymph nodes of the mesentery and those around the celiac axis and pancreas are bright yellow and soft. The reticulo-endothelial cells of the mesenteric nodes show large amounts of neutral fat and lipoids. The hilar nodes in the mediastinum are anthracotic and contain similar tissue; no other change.

"The brain shows no gross lesion. The vessels at the base show no sclerosis. The hypophysis and pineal gland are grossly normal.

"There is only a very small amount of fat present in the subcutaneous tissue, in the mesentery and in other parts where fat might normally be found.

Diagnoses: 1. Atrophy of the thyroid and pancreas. 2. Huge megacolon. 3. Carcinoma of the sigmoid with metastases to the liver. 4. Myxedema (clinical). 5. Diabetes mellitus (clinical)."

A complete discussion of the various aspects of this association of myxedema and diabetes will be found in the papers of Shepardson and Wever,[9] Weinstein [10] and of one of us.[1] Others [11, 6, 2, 5, 3, 7, 4, 8] have also commented upon the effect of hyper- and hypothyroid states on carbohydrate metabolism. Although the occurrence of myxedema and diabetes in the same patient is probably wholly fortuitous, there seems to be no doubt that, once established, there is a reciprocal reaction of the secretions of the two glands concerned. It is not apparent that the diabetes influences the myxedema, but it is certainly evident that the myxedema modifies the diabetes. That is, whenever the metabolic rate is increased by the administration of thyroid, the carbohydrate tolerance is markedly reduced. In spite of this, of the two recorded deaths neither was due to either diabetes or to the effects of myxedema. In Weinstein's case death was said to be due to heart failure of congestive type, and at post mortem high grade arteriosclerotic aortic valvular disease was found—apparently not a myxedema heart, although no other details of the pathological examinations of the cardiovascular system were given. Our case died of intestinal obstruction.

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COARCTATION OF THE AORTA, DISSECTING ANEURYSM, AND ANEURYSMAL DILATATION OF THE LEFT VERTEBRAL ARTERY; REPORT OF A CASE*

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New York, N. Y.

Although several unusual, indeed, almost unique features alone justify the publication of this case, a more compelling motive, the equally rare correct appraisal of the situation, is responsible. Only 10 per cent of the cases of aortic coarctation have been recognized ante mortem and its discovery at postmortem examination remains a "surprise d'amphitheatre." One of us (L. J. B.) has had the opportunity to make the presumptive diagnosis of coarctation of the aorta twice within two years on the basis of hypertension, marked differences in the blood pressures in the arms and legs, notching of the lower borders of the ribs and absence of the aortic arc with dilatation of the ascending aorta. However, the coarctation was completely unsuspected in the present case.

The same general situation prevails in respect to dissecting aneurysm. Less than 5 per cent of the reported cases have been recognized ante mortem. The typical features of this case permitted belated but ante mortem recognition. The combination of coarctation of the aorta and rupture (or dissecting aneurysm) is evident in 16 per cent of the cases of isthmus stenosis reported in the literature.

Since the circulation for the lower half of the body is derived almost entirely from the subclavians in aortic coarctation, it is not surprising that the vertebral arteries, representing the first subclavian branches and participating in the formation of collateral circulation, should become elongated and dilated. However, distinct aneurysmal dilatation of one vertebral artery, sufficient to induce partial pressure atrophy of the cerebellum, as occurred in this case, is extremely unusual. While this dilatation probably represented an associated vascular anomaly, it did not occur at the bifurcation of a vessel and did not represent a "congenital miliary aneurysm" whose rupture accounts for the hemiplegia.

A brief résumé of the significant points follows:

Case Report

A. C., a 57 year old housewife, entered the Metropolitan Hospital October 8, 1936, at 8:30 p.m., complaining of weakness and of very intense pain in the right abdomen and right kidney region.

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From the Department of Medicine, The New York Medical College and Flower Hospital and the Medical Service of the Metropolitan Hospital, New York City.

Four years before she had experienced a very severe epistaxis. At that time her physician discovered hypertension. Dyspnea on exertion, edema of the ankles at night, and nocturia two to three times have been noted during the last two years. Menopause occurred 13 years ago; venereal infections were denied. No pregnancies.

One week prior to admission while doing housework, she was suddenly seized with excruciating pain in the right lumbar region. This pain radiated downwards. At the same time she noted severe precordial pain, a choking sensation in the neck, and these were accompanied by vomiting. In a few hours the choking sensation and vomiting ceased but the pain and weakness persisted. She applied mustard plasters to the back and chest for the relief of pain but without success.

Examination: The patient was a well developed obese white female lying in bed apparently in pain. Slight cyanosis of the lips and tip of the nose was observed. Neither dyspnea nor orthopnea was evident. Over the left lower anterior chest and over the entire lumbar region there was a large first degree burn (mustard plasters).

Head: No scars, deformities, nor abnormalities. *Eyes:* Pupils equal and react to light and accommodation. No nystagmus, strabismus nor disturbance of extra-ocular muscle movements. The arteries of the fundi are sclerotic, but no hemorrhages are present. *Nose:* Septum deviated to the right. Mucous membranes normal. *Mouth:* Teeth stained and carious; tongue coated; throat moderately injected.

Chest: Breasts large and pendulous but no masses. Chest expansion free and equal; no abnormal pulsations; lungs negative. *Heart:* P.M.I. in the sixth interspace at the anterior axillary line. No murmurs or thrills elicited. The aortic second sound was accentuated. The cardiac rhythm was regular, rate 100. The heart sounds were distant. The radial pulses were equal, synchronous, and regular; blood pressure 180 systolic and 120 diastolic in both arms.

Abdomen: No viscera could be palpated and there was no evidence of free fluid. No tenderness, rigidity or masses. *Back:* Marked tenderness in both lumbar regions; otherwise negative.

Extremities: No edema or clubbing; the normal reflexes were present and no pathological reflexes could be elicited.

Impression: On admission she was regarded as an instance of hypertensive cardiovascular renal disease developing upon an arteriosclerotic basis with probable renal arteriolar sclerosis. It was thought that she should be regarded as a hypertensive angina pectoris rather than a coronary infarction in view of the maintenance of the high blood pressure level. Lumbar radiation of pain in coronary infarction has not been encountered by the writers and suggested a renal lesion, possibly nephrolithiasis. As liberal amounts of morphine scarcely blunted the pain it was decided to defer further investigation until the patient was more comfortable.

Throughout the following day the pain was less severe. Blood chemical tests were normal. The blood Wassermann test was three plus. The white blood cell count was 13,200 with 80 per cent polymorphonuclears. In view of the evident improvement it seemed advisable to postpone electrocardiographic examination.

At 8:00 p.m. that night she again complained severely of intense aching pain in the lumbar region and severe aching pain in both sides of the chest. The blood pressures remained unchanged. At 11:00 p.m. the patient became stuporous and was unable to speak. There was constant moaning, and rubbing of the lumbar region with her right hand. Respirations were rapid and shallow. The face was pale and the body covered with cold sweat. Soon there appeared a complete paralysis of the left arm, leg, and face. The pupils were equal but the right reacted poorly to light. Within a few minutes no pulse could be felt at the left wrist and no blood pressure could be obtained in this arm. The blood pressure on the right arm was now 200 systolic and 75 diastolic and the pulse was full and regular. On the basis of the

symptomatology now present a presumptive diagnosis of dissecting aneurysm was suggested (Dr. Carl Nussbaum). At 12:30 p. m. she had a generalized convulsion and died.

An abbreviated account of the post mortem follows (courtesy of Dr. Andrea Saccone):

The body is that of a well developed white adult female. Rigor mortis is complete; livor mortis present posteriorly. The hair is grey. The pupils are equal, regular and in mid-dilatation. Lips, finger tips and toes are cyanotic. A large erythematous area is noted over the entire lumbar region.

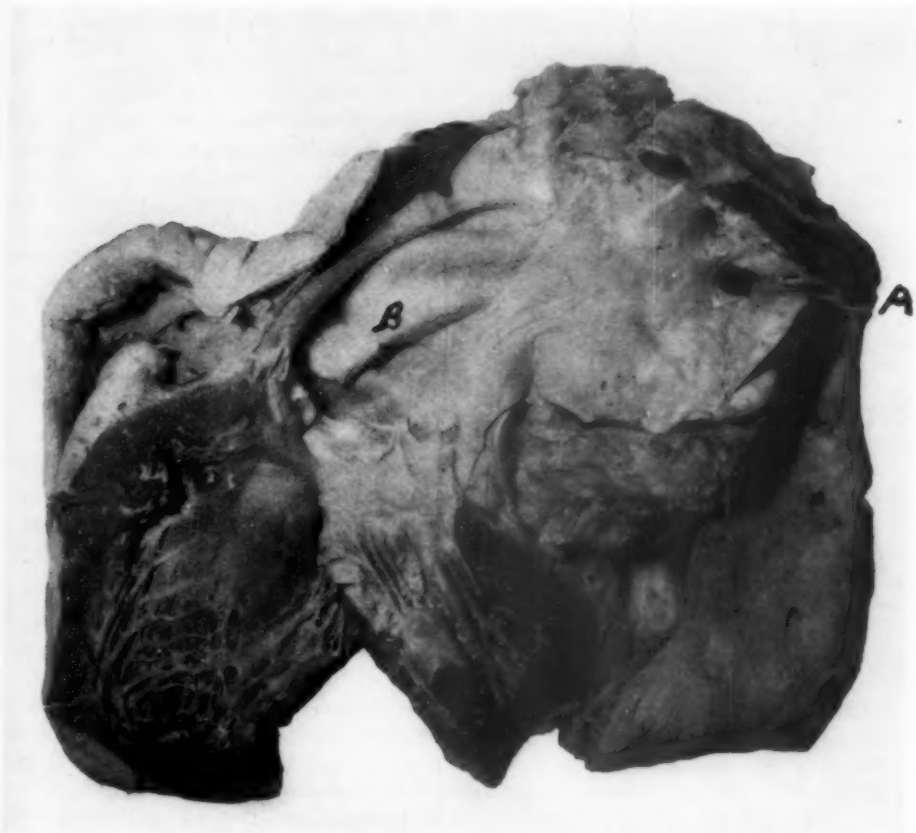

FIG. 1. The coarctation may be seen at the upper right of the illustration (*A*). The large vessels of the arch, normal in number and arrangement but enlarged owing to their participation in the formation of anastomoses, are evident just to the left of the coarctation. The atheromatous patches in the intima can also be identified. Proceeding to the left is the longitudinal tear in the aorta (*B*); below this, two of the aortic cusps are visible. (This illustration became available through the courtesy of the Medical Examiner's Office, New York City. The specimen has been placed in the museum of that department.)

On mid-section the subcutaneous fat measures 1½ cm. in thickness. There is no free fluid either in the abdominal or pleural cavities. The pericardium contains 300 c.c. of blood, most of which is clotted and envelops the heart.

The epicardium is infiltrated with a moderate amount of fat. The coronary vessels are tortuous. The right heart is soft, the left firm. The muscle of the right

ventricle measures 3 mm. in diameter while that of the left ventricle is 1½ cm. in thickness. There is some hardness at the base of the aortic valve but its cusps are normal in number, size and arrangement. The orifices of the coronary vessels are normal. About 2.5 cm. above the line of closure of the aortic valves there is a longitudinal tear in the intrapericardial portion of the ascending aorta. This tear extends through the aorta and is the source of the blood in the pericardial cavity. The entire aorta, the branches of the arch and both iliac arteries have been dissected by a large accumulation of blood between the intima (?) and media. The innominate, carotid and left subclavian are very large and branches of the left subclavian are particularly enlarged and show well developed anastomoses. No anomalous branches from the aorta were noted. The intima is covered by many scattered atheromatous patches. At the isthmus of the aorta, just at the ligamentum arteriosus, there is a decided narrowing of the lumen by a firm ring-like thickening so that the lumen of the aorta at this point will just admit a lead pencil. The diameter of the aorta above the coarctation is considerably greater than the diameter below. The mitral and tricuspid valves are normal. Both auricular appendages are clear. The myocardium is uniformly dull brown in color.

The right lung is soft in consistency and dark in color. On section some bloody fluid oozes from the cut surface. The left lung is similar. The gall-bladder is filled with a small amount of thin bile. The liver cuts easily and shows a moderate nutmeg appearance. The splenic capsule is wrinkled and the pulp soft. The pancreatic parenchyma shows congestion. The duodenum is edematous and the remainder of the intestine reveals congestion. The adrenals are separated into two layers by edematous hemorrhagic fluid. The kidney capsule strips easily leaving a granular surface with prominence of the stellate veins. The markings are lost. The cortex is narrow and irregular and the entire parenchyma markedly congested. Uterus and adnexa are normal. The bladder mucosa is congested.

Some thickening of the bone is noted upon removal of the calvarium. The dura as well as the leptomeninges is markedly congested. There is moderate cloudiness of the sulci. The left vertebral artery is markedly dilated and tortuous and forms a short fusiform dilatation, 1½ cm. in diameter. The inferior surface of the left cerebellar hemisphere is correspondingly indented by the dilatation of this vessel. The cerebellum is asymmetric and the right vertebral artery is thinner than the left. The left lateral ventricle is slightly enlarged; no change at the base of the fourth ventricle or in pons. The remainder of the brain reveals a lacunar stage of cerebral arteriosclerosis with lesions located principally in the gray nuclei of the right hemisphere.

Anatomical Diagnosis: Hemopericardium; rupture of the aorta; dissecting aneurysm of the aorta, branches of the arch and iliac arteries; coarctation of the aorta, fusiform dilatation of the terminal portion of the left vertebral artery; generalized arteriosclerosis; pressure atrophy of the inferior surface of the left cerebellar hemisphere; passive congestion of the lungs; cloudy swelling of the liver; passive congestion of the spleen; chronic diffuse nephritis with terminal congestion; congestion of brain.

Upon microscopic examination of the aorta with special reference to the vasa vasorum no evidence of syphilis or other lesion could be found. The intima was dissected and degenerated near the tear with an adherent clot of fibrin; elsewhere it is thrown into irregular folds. Near the tear the elastic membrane is completely torn and there is a faint necrosis of the media which elsewhere merely shows dissection. The adventitia is negative. Examination of the kidney sections shows a chronic glomerular nephritis with terminal nephrosis.

Comment

If coarctation of the aorta had been suspected it is probable that a marked difference in the blood pressures of the arms and leg would have been found. However, less than 3 per cent of the reported instances of coarctation, in itself an uncommon anomaly, have been found in females over 50 years of age. Apparently the oldest age of rupture of the aorta associated with coarctation in a female hitherto reported was thirty. Moreover if persistent differences in the arm blood pressures had been found early in this case, we would have been inclined to attribute them to a specific mesaortitis.

Inexplicable hypertension in youths is extremely suggestive of coarctation; apparently this possibility must be considered, even if rarely, in older individuals. It is often stated that glomerular nephritis must be eliminated as a cause of hypertension in suspected coarctation; in this case both lesions existed. If the dissection of the renal arteries and a more protracted course had permitted, uremia might have further complicated the puzzling picture.

Among the signs commonly attributed to coarctation the following were absent in this case: disproportion in size, color, and temperature between the upper and lower half of the body; abnormal pulsations in the neck, back and intercostal vessels; palpable intercostal arteries; parasternal post-systolic murmur. Notching of the lower border of the ribs was not studied by roentgen-ray, but none was found at post mortem. The intercostal vessels did not play an important rôle in the anastomosis. Dilatation of the ascending portion of the aorta would have been found on roentgen-ray but we would probably have attributed it to a non-existent luetic aortitis. Absence of the aortic arc in the second left oblique position ought to have been present. Other signs such as retardation or diminution of the femoral pulse, small oscillometric waves, increased reactive hyperemia in the poorly circulated extremities, the low fall and later, long duration of increased superficial temperature during and after obstruction to the circulation, the long duration of the fall of blood pressure in the lower limbs after application of obstruction to circulation in the upper half of the body would have been equivocal in the presence of dissecting aneurysm.

In retrospect our diagnostic failure may be assigned chiefly to two prevalent mistakes: Our neglect to determine blood pressures in the upper and lower extremities routinely in cases of hypertension; our failure to think of the possible presence of an unusual lesion.

The symptomatology of the dissecting aneurysm in this case was typical. The immediate onset of maximum and severe pain; its unusual radiation (or localization) to below the mid-lumbar region; the nausea and vomiting (aortic depressor nerve?); the maintenance of the high level of blood pressure with regular, scarcely elevated heart rate; the development of hemiplegia and the absence of pulse in one arm may be mentioned in passing. The persistent and recurring back pain may be attributed to marked dissection of the intercostal arteries. Supra-pubic cyanosis, said to be present in aortic obstruction at the bifurcation and arising from a "rider" embolus, was absent.

Hemiplegia occurs not infrequently in coarctation of the aorta as the result of cerebral hemorrhage. This may be due to rupture of an intracranial "congenital aneurysm." In this case the hemiplegia may be attributed partly to the occlusion of one carotid artery by the dissection of its walls, partly to the cerebral

edema. Partial or complete disappearance of the carotid pulsation ought to have been elicited in this case but on this point the record is silent.

A careful study of the vasa vasorum failed to reveal any evidence tending to incriminate syphilis as a factor in producing the dissecting aneurysm. Nevertheless it may have facilitated the evolution of the catastrophy. Evidence was also lacking of a *mesaortitis dissecans* in the sense of Babes and Mironescu. The medial changes of Gsell and Erdheim's *medionecrosis aortae idiopathica cystica* were likewise absent. The minute hemorrhages from the vasa vasorum and small mural hematoma described by Moriani were not present. The thinned and faintly staining media together with the fragmented and broken elastic membrane are consistent with the mechanically conditioned transformation of the aortic wall in the presence of persistent hypertension (as described by Einhauser). It does not seem logical to speak of a constitutionally weak aorta when it resisted the onslaught of hypertension for more than one half a century. It is of interest to note that the aortic tear occurred at Oppenheim's point of maximum functional strain of the aorta. In contrast to most cases the tear was longitudinal rather than transverse. This is alleged to facilitate hemopericardium rather than extensive dissection. The presence of concomitant vascular anomalies of constitutional origin is strongly suggested by the aneurysmal dilatation of *one* vertebral artery.

Finally increasingly distant heart sounds with maintenance of the blood pressure in a case of dissecting aneurysm (or coarctation) should justify the diagnosis of hemopericardium even in the absence of increased cardiac dullness. The absence of cardiac hypertrophy and dilatation in the presence of prolonged hypertension, as in this case, should be provocative of thought.

Summary

A case of the adult type of coarctation of the aorta, dissecting aneurysm and fusiform dilatation of the left vertebral artery is presented. Attention is directed to our failure to recognize the coarctation rather than our success in appraising the dissecting aneurysm. Diagnostic errors occur in both lesions with disturbing frequency which may be diminished by popularizing consideration of these lesions as diagnostic possibilities.

EDITORIAL

THE VALUE TO CLINICAL MEDICINE OF EXPERIMENTAL STUDIES ON THE LIVER

It is difficult for the clinician interested in hepatic disease to overestimate the debt owing to laboratory workers who have so diligently studied the pathologic physiology of the liver. Clinical knowledge of hepatic disease, having been almost at a standstill for fifty years, is now being immensely enriched by the contributions of physiologists and biological chemists who have, first, fully informed us of the functions of the liver and later demonstrated its reparative and regenerative properties, its extraordinary reserve functional capacity and, most recently, the activities of the organ in maintaining normal internal environment.

A large part of the success attained by the physiologists has been attributable to their ability to reproduce in the experimental animal two of the common clinical affections, obstructive jaundice and parenchymatous injury. The pathology and physiology of the former condition, easily produced by ligature of the bile ducts, has now been thoroughly studied from its inception to its end stage of obstructive biliary cirrhosis. The simulation of parenchymatous lesions has been a more difficult matter but it is now possible to reproduce an almost perfect experimental counterpart of atrophic cirrhosis by the continued administration of carbon tetrachloride. The effects of variations in the diet on the course of experimental hepatic disease, and on the ability of the liver to repair itself and regain its function after an almost lethal injury have been fully demonstrated by this means.

The protective effect of high carbohydrate diets in poisoning from chloroform and phosphorus, first shown years ago by Opie and Alford,[1] is now known to be equally effective in retarding the development of hepatic damage induced by biliary obstruction and carbon tetrachloride. Diets of high fat content recently have been shown by Bollman [2] to have an opposite effect. For instance, it is virtually impossible to produce any significant hepatic lesion in the dog by administration of alcohol if the animal is on a mixed diet; with a high fat diet marked fatty degeneration can be produced by this means. Such a diet given alone, without any hepatotoxic agent, also will lead eventually to fatty metamorphosis. Such fatty livers are easily injured by any hepatic poison and undergo necrosis and parenchymatous degeneration even with minimal insults. The only known means of protection against the fatty change produced by dietary means and by certain specific poisons are three: an increased intake of carbohydrate, the adminis-

[1] Opie, E. L., and Alford, L. B.: The influence of diet upon necrosis caused by hepatic and renal poisons. I. Diet and the hepatic lesions of chloroform, phosphorus, or alcohol, Jr. Exper. Med., 1915, xxi, 1–20.

[2] Bollman, J. L., and Mann, F. C.: The physiology of the impaired liver, Ergebn. d. Physiol., 1936, xxxviii, 445–492.

tration of lecithin or one of its components, choline, and the use of a pancreatic hormone designated as "lipocaic" by its discoverer, Dragstedt [3] and his associates.

The relation of the last two mentioned substances to fatty change in the liver is an interesting chapter in itself. The development of hepatic insufficiency in pancreatectomized dogs whose diabetes was controlled by insulin led to an investigation of the morphology of the liver; it was first shown by MacLeod and his collaborators [4] and later by Best, Ferguson and Hershey [5] that the underlying lesion was marked fatty degeneration. Similar changes in the hepatic parenchyma are known to occur in the diabetic human subject [6] and in patients with pancreatic atrophy produced by lithiasis. In the pancreatectomized dog, lecithin or choline has been shown to exert an inhibitory effect on this process; recently Dragstedt and his associates [3] have shown that it is possible to extract from the pancreas a hormonal substance which inhibits deposition of fat in the liver after pancreatectomy. This preparation has been used effectively in treatment of one human subject with pancreatic stone and a presumably fatty liver and may have some further clinical application in severe diabetes and in acute fatty infiltration of the liver produced by poisons.

Do these fatty changes constitute the forerunners of nodular cirrhosis? Ordinarily they do not lead to any permanent hepatic lesion in the experimental animal but knowing the extreme vulnerability of the fatty liver, it is reasonable to assume that any added toxic factor might easily lead to the development of parenchymatous degeneration and nodular hyperplasia. It is clear that more attention will have to be paid to the relation of the diet to hepatic disease and that regulation of its fat and lecithin content may well find a place in the therapeutics of hepatic disease.

From the chemical and physiologic laboratories some light has been cast in recent years on the mechanisms by which ascites is produced. It has been demonstrated that the condition does not depend on portal back pressure alone, although in most hepatic diseases associated with ascites there are gross evidences of interference with portal blood flow. Ascites sometimes appears spontaneously as a terminal development in the animal with long-continued experimental biliary obstruction and in such animals may be induced almost at will by oral administration of meat extractives which are virtually free of protein. The same situation exists in animals with cirrhosis induced by carbon tetrachloride but in neither instance is there any satisfactory explanation of why these innocuous meat extracts have this puzzling effect. The spontaneous appearance of fluid, on the other hand, is

[3] Dragstedt, L. R., Van Prohaska, John, and Harm, H. P.: Observations on a substance in the pancreas (a fat metabolizing hormone) which permits survival and prevents liver changes in depancreatized dogs, Am. Jr. Physiol., 1936, cxvii, 175–181.

[4] Allan, F. N., Bowie, D. J., MacLeod, J. J. R., and Robinson, W. L.: Behavior of depancreatized dogs kept alive with insulin, Brit. Jr. Exper. Path., 1924, v, 75–83.

[5] Best, C. H., Ferguson, G. C., and Hershey, J. M.: Choline and liver fat in diabetic dogs, Jr. Physiol., 1933, lxxix, 94–102.

[6] Root, H. F.: Diabetic coma and acute pancreatitis with fatty livers, Jr. Am. Med. Assoc., 1937, cviii, 777–780.

thought to depend on at least three factors; the degree of parenchymatous hepatic injury, interference with portal circulation and reduction of plasma proteins. A slight but progressive fall in concentration of these last-named substances occurs almost as a rule in hepatic disease of any type, both experimental and clinical and, more significantly, there is a proportionately greater fall in serum albumin than in total protein; the globulin fraction may be either normal, increased, or decreased. Without entering into detailed discussion of the reasons for this development of hypoproteinemia, it may be said that the available evidence points to failure of the liver to furnish albumin or albumin-producing substances, with a disturbance in the dynamic equilibrium existing between stored and circulating protein.[7] The obvious result is a fall in the colloid osmotic pressure of serum, a condition which favors transudation in regions of venous stasis. The full extent of this decrease in the osmotic properties of serum of patients with hepatic disease has only recently been appreciated. Butt and Keys [8] have measured the colloid osmotic pressure by a modification of the method in which a membrane bag is used and have shown reductions to as little as half of the normal value; the observed pressures of practically all patients with ascites or edema are below the theoretical level at which transudation may occur. Furthermore, the figures of the named investigators show clearly that the observed osmotic pressure is not in linear relation to the total protein content of serum and that in about a third of the cases, sharp reductions in colloid osmotic pressure are noted even when the value for total protein is normal. Bollman's [9] unpublished studies on the effects of plasmapheresis in animals with experimental cirrhosis have in general confirmed the above-mentioned observations, but they appear to show that there is no constant level of colloid osmotic pressure at which ascites invariably occurs. In other words, there are other variable factors presumably involving such matters as pressure in mesenteric capillaries and the degree of hepatic damage. The effects of meat extracts described in an earlier paragraph may involve such factors. Measurements of pressure in the portal system of subjects with cirrhosis are not as yet available, but such studies doubtless will be undertaken by physiologists, in the experimental animal. The problem of electrolyte and water distribution between circulating fluids and tissue fluids must also be investigated further since changes in osmotic pressure of the order of magnitude observed by Butt and Keys can scarcely be without some effect on the hydration and electrolyte content of individual cells.

Some of the major clinical problems yet to be solved by students of hepatic disease are concerned with the nature of hepatic insufficiency and with the cause of the hemorrhagic diathesis. On the first matter little information is available although the metabolic disturbances which occur in

[7] Holman, R. L., Mahoney, E. B., and Whipple, G. H.: Blood plasma protein given by vein utilized in body metabolism. II. A dynamic equilibrium between plasma and tissue proteins, Jr. Exper. Med., 1934, lix, 269–282.

[8] Butt, H. R., and Keys, Ancel: Colloid osmotic pressure; studies of normal individuals and of those with hypoproteinemia, Proc. Staff Meet. Mayo Clinic, 1937, xii, 566–570.

[9] Bollman, J. L.: Unpublished data.

hepatectomized animals and in those with extreme hepatic injury have been extensively studied. One fact is certain; no form of hepatic damage, clinical or experimental, even approximates the picture of absolute hepatic insufficiency produced by total removal of the liver. The major metabolic properties are almost universally preserved even with maximal hepatocellular destruction. The most favored hypothesis of clinical hepatic insufficiency is that the detoxifying function of the organ is so altered that the increased susceptibility to endogenous and exogenous toxins produces a fatal issue before the entire function of the liver is lost.[2] The vulnerability of the damaged liver to infections, anesthetics, and hepatotoxins may be cited in support of this hypothesis, as well as the fact that the symptoms of the Eck fistula animal seem to be clearly attributable not so much to diversion of blood flow as to failure of detoxification. In addition to the hypothetical failure of this function, one must concede that other factors enter into the clinical picture of hepatic insufficiency. In the occasional case there are striking changes in the chloride content of blood and in the acid-base equilibrium; the factor of anoxic anoxemia which is quite constantly present in advanced hepatic disease also may not be without significant effect especially on those tissues which are particularly sensitive to oxygen want. There is good reason to believe that the condition of hepatic insufficiency is a reversible one, and the occasional recovery of a patient from profound hepatic coma gives hope that its physiologic nature may be known and controlled.

So far as the problem of hemorrhage in hepatic disease is concerned, it seems to be one manifestation of hepatic insufficiency, or at least the two often occur simultaneously. All factors necessary for normal coagulation of blood such as calcium, fibrinogen and thromboplastin are presumably present in normal amounts, leaving prothrombin as the only variable. Exact methods for the determination of these substances have not been developed but studies from a number of laboratories indicate that the hemorrhagic state in hepatic disease may depend on deficiency of prothrombin alone[10] and that this in turn may be dependent on the exclusion of bile from the alimentary tract or on disruption of the mechanism by which prothrombin or some precursor is stored.

The possible relation of prothrombin to the hypothetical "Koagulations vitamin," the existence of which has been only recently recognized, was first brought under consideration by biochemical studies of the diseases of domestic animals. In such widely differing conditions as a specific deficiency disease of chicks, the toxic sweet-clover disease of cattle, prolonged obstructive jaundice and complete external biliary fistula, the prothrombin of the blood is reduced. Since the first two conditions respond to administration of vitamin K, it is reasonable to hope that the last two may be similarly affected. Chemically, prothrombin and vitamin K appear to have

[10] QUICK, A. J., STANLEY-BROWN, MARGARET, and BANCROFT, F. W.: Study of coagulation defect in hemophilia and in jaundice, Am. Jr. Med. Sci., 1935, cxc, 501–511.

little in common, but there is indirect evidence pointing to some obscure interrelation between the two substances. Clinical data are almost completely lacking but the theoretical possibilities are exceedingly attractive.

Certain other fields of purely clinical research in hepatic and biliary disease which are being developed can only be mentioned here. Studies on the so-called biliary dyskinesia to which Westphal,[11] Ivy [12, 13] and McGowan [14] and his collaborators have contributed are furnishing an explanation of some hitherto obscure visceromotor phenomena as well as helping to explain the mechanism of the sphincter of the common duct and its relation to biliary pain.

The application of accurate physiologic methods to the clinical study of hepatic and biliary disease obviously is increasing our comprehension of the subject, but it is apparent that many crucial problems will have to be solved, not at the bedside alone but by the clinician and the experimental pathologist working in coöperation. The clinical application of facts already known and of others yet to be unearthed doubtless will be a slow process but it is equally certain that their utilization eventually will serve to expand present diagnostic and therapeutic horizons. Just as we owe our present facilities for the care of the diabetic patient to studies on the dog, so we may eventually attain some mastery of hepatic disease by continuation of experimental studies which at first seem far removed from the field of clinical medicine.

ALBERT M. SNELL

[11] WESTPHAL, KARL: Muskelfunktion, Nervensystem u. Pathologie der Gallenwege: I. Untersuchungen über den Schmerzanfall der Gallenwege und seine ausstrahlenden Reflexe, Ztschr. f. klin. Med., 1923, xcvi, 22–51. II. Experimentelle Untersuchungen über die nervöse Beeinflussung der Bewegungsvorgänge der Gallenwege, Ztschr. f. klin. Med., 1923, xcvi, 52–94. III. Die Motilitätsneurose der Gallenwege und ihrer Beziehungen zu deren Pathologie, zur Stauung, Entzündung, Steinbildung u.s.w., Ztschr. f. klin. Med., 1923, xcvi, 95–150.

[12] IVY, A. C., VOEGTLIN, W. L., and GREENGARD, HARRY: The physiology of the common bile duct; a singular observation, Jr. Am. Med. Assoc., 1933, c, 1319–1320.

[13] IVY, A. C., and SANDBLOM, PHILIP: Biliary dyskinesia, ANN. INT. MED., 1934, viii, 115–122.

[14] MCGOWAN, J. M., BUTSCH, W. L., and WALTERS, WALTMAN: Pressure in the common bile duct of man; its relation to pain following cholecystectomy, Jr. Am. Med. Assoc., 1936, cvi, 2227–2230.

REVIEWS

Observations of a General Practitioner. By WILLIAM N. MACARTNEY, M.D. 478 pages; 21 × 15 cm. The Gorham Press, Boston. 1932. Price, $3.00.

Physicians actively engaged in the practice of medicine will like this salty volume with its first hand observations on disease and human beings interspersed with humorous anecdotes of varying degrees of savoriness. Those who are hospital physicians will be interested in the different types of disease seen in practice. There is much to think about in these chapters for the author includes his medical philosophy as well as his medical experience. He writes in vigorous and pungent short sentences and says his mind plainly. Therapy is particularly worth consideration because one feels he applied it himself and observed the results personally without an intervening screen of assistants, interns and nurses.

Altogether this is an entertaining and instructive book. Most of us will heartily disagree with a large number of the author's ideas but we will think all of them worth considering and tuck many a suggestion away in our mind for future trial.

M. C. P.

Der Blutdruck Des Menschen. By ESKIL KYLIN. 322 pages; 23.5 × 16 cm. Verlag von Theodor Steinkopff, Dresden and Leipsiz. 1937. Price, RM 24.

The purpose of this book is to present the author's views as to the problem of abnormalities of blood pressure. It is therefore a discussion of the mechanisms involved in the maintenance of normal pressure and in the causation of hypertension and hypotension. It is not concerned except in a secondary way with the symptomatology of blood pressure derangements nor with therapeutic procedures. The first section deals with normal blood pressure, arterial, capillary and venous. This is followed by a very interesting discussion of modern concepts of blood pressure regulation; divided into chapters on central factors in blood pressure regulations, on peripheral mechanisms, and on the rôle of endocrine organs.

The subject of arterial hypertension is introduced by a section devoted to a general discussion of the varieties of disturbances or lesions which may lead to a higher level of blood pressure. The author is a strong advocate of the belief that the hypophysis secretes through an ependymal lined canal into the third ventricle. The character of the secretion alters the irritability of hypothalamic blood pressure regulating centers, and plays therefore a major rôle in essential hypertension. The evidence in favor of these views is marshalled in an ingenious way. The author devotes considerable space to an attempt to minimize the relationship between kidney lesions and hypertension. It is evident that he is not well acquainted with the foreign literature since he omits the fundamental experiments of Goldblatt and the most important references on the relation of polycystic disease to hypertension.

In the discussion of major clinical varieties of hypertension the author subdivides them into capillary and arterial forms of hypertension. He believes that diffuse glomerulo-nephritis is primarily a generalized capillary disease. No convincing proof of this assertion is offered.

Enough has been said perhaps to show that this volume will interest all students of the problem of hypertension. The author is learned, original and somewhat prejudiced in favor of his own opinions. Every internist can study the results with profit.

M. C. P.

The Cardiac Glycosides. By ARTHUR STOLL, D.Sc., M.D. 80 pages; 25 × 17 cm. Pharmaceutical Press, London. 1937.

This treatise comprises three lectures delivered by Professor Stoll in the College of the Pharmaceutical Society of Great Britain under the auspices of the University of London. The first of these lectures is devoted to the importance of sugars in the plant economy and the classification of glycosides including a series of definitions of terms. In this lecture also the specific glycosides of digitalis and strophanthin are discussed. Great stress is laid on the structure of the sugars isolated from the cardiac glycosides. The historical features of the chemical and clinical events of significance in the development of these compounds are referred to in a very interesting manner.

The second lecture treats of the glycosides of squill and the hydrolysis and products of hydrolytic cleavage of scillaren A. The structures of the aglycones are discussed and compared. These structures are shown to be phenanthrene derivatives and related to the bile acids, sex hormones and toad venoms. The schemes of cleavages and the complex structures of the aglycones are especially well elucidated.

In the third lecture the author discusses the digitalis glycosides with special reference to botanical species variation. Methods of extraction are critically evaluated. The cardiac principles from *digitalis purpurea, ambigua* and *lanata* are compared. Comprehensive studies on the extraction of Digilanid from *digitalis lanata* are described. The author concludes that this crystalline glycoside is the only chemically pure digitalis glycoside of constant constitution. Its therapeutic dose for man orally is 0.75 mg. daily. It is available also for intramuscular and intravenous medication.

The style of the author is lucid and the subject matter timely.

J. C. K., JR.

Exophthalmic Goiter and Its Medical Treatment. By ISRAEL BRAM, M.D. Second Edition. 456 pages; 25 × 17.5 cm. C. V. Mosby Company, St. Louis. 1936. Price, $6.00.

In his preface to this work, the author describes it as a "treatise on the etiology, diagnosis, and principles of the medical treatment of exophthalmic goiter, based on personal experience with over 5000 cases of this disease, observed within a period of over 25 years." In a footnote, he states that this number is included within the total of approximately 16,000 goiter cases observed.

After reading the book, one is forced to the conclusion that the author has been almost miraculously successful in curing a large series of cases of exophthalmic goiter, and in a strikingly short time. Statistically, he reports only 2600 cases, so that one wonders as to the results in the remaining 2400. Apparently 90 per cent of the 2600 cases were completely cured, as they were all well after being followed for periods of from 3 to 20 years; 10 per cent had minor residual symptoms. There were, therefore, no deaths in this group. Sixty-seven per cent of the cases were discharged from treatment after six months; 17 per cent are reported as continuing their customary duties while under treatment; and another 44.9 per cent abstained from their work for three months or less.

The author feels that surgical interference is usually contraindicated, and states that indications for thyroidectomy occur in a little over 2 per cent of all patients with Graves' disease. Surgery and radiation he classifies as local measures, to be used rarely. He places great emphasis on the danger and frequent occurrence of postoperative myxedema, and gives the impression that exophthalmic goiter with myxedema is very common in patients treated by methods other than his own.

One would feel more confidence in the author's statements if there were not so many obviously weak points in the book. The illustrations, 79 in number, are limited to photographs of patients, either before, or in many cases, before and after treat-

ment. The absence of photographs of histological sections of the thyroid gland is surprising. Disappointing, too, is the section on basal metabolism; the term "basal metabolic rate" is not defined, is not described as a measurement of heat production of the body, nor is there any discussion of methods of determination of the rate.

Literature is extensively quoted, but superficially reviewed, and opinions are given without reference to the date of the article. Many antiquated observations are quoted, and it is usually impossible to tell their date from the text.

In the final chapter, 55 cases are reported fairly fully except that the details of treatment are omitted.

In the section on treatment, quinine is emphasized as a very important drug. The therapeutic value of glandular extracts is reviewed, but, again, the author frequently quotes antiquated studies, for instance, in the discussion of the use of adrenal cortical extracts. In this paragraph, he advocates the oral administration of pills of glycerinated cortical extracts. Later, he advocates the oral use of ovarian residue in the presence of amenorrhea in the female.

On the whole the book does not appear to be a safe guide. The opinions expressed are contrary to the experience of most physicians and the data furnished will not induce those with an analytic faculty to alter their views.

T. N. C.

Pediatric Dietetics. By N. THOMAS SAXL, M.D. 565 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1937. Price, $7.00.

Various works dealing with the diets of individuals in the pediatric age, have in the past been limited mostly to infant feeding. The nutritional aspects of the child over two years of age has been relegated to the domain of adult nutritional problems. Dr. Saxl has presented the entire subject of pediatric dietetics in a separate volume. The appearance of a work of this type is timely, for to quote Dr. De Sanctis in his foreword to this volume "Lay periodicals, press and radio have persistently encouraged various types of diets for adults. The vast majority of these are scientifically unsound and unfortunately have been applied to children."

The subject matter of this volume has been presented in three parts, subdivided into sections. Into the first part the author condenses the mechanics and chemistry of digestion during infancy. Explanation of the *modus operandi* and indications for use of the various basic constituent foods are also included in this section. A comprehensive summary of accepted proprietory foods is also made. In addition a brief statement of the nature, source and therapeutic use of vitamins is given.

Part II deals with infant feeding, a section being devoted to breast feeding and one to the artificial method.

Part III deals with dietetic management of pediatric diseases. Physicians interested in various conditions have collaborated with Dr. Saxl in the presentation of this section. To those not sufficiently familiar with metabolic processes in pathological conditions this section will clarify a number of disease processes.

The appendix is composed of numerous receipts, tables of weight, height, and foods. Also, incorporated is a very exhaustive bibliography.

The work in its entirety is written in a uniformly easy manner. Much of the material is to be counted as superfluous, and much could be shortened without destroying completeness. The volume represents a needed contribution, dealing with the nutritional needs of the child in disease and health. It is a useful addition to the library of the practitioner.

J. E. B.

COLLEGE NEWS NOTES

Gifts to the College Library

The following gifts to the Library of Publications by Members are gratefully acknowledged:

Books

Dr. Kenneth E. Appel (Associate) and Dr. Edward A. Strecker (Fellow), Philadelphia, Pa., "Practical Examination of Personality and Behavior Disorders: Adults and Children";
Dr. Jacob Gutman (Fellow), Brooklyn, N. Y., Twelfth Supplement to "Modern Drug Encyclopedia";
Dr. George B. Lake (Associate), Waukegan, Ill., "Parenteral Therapy."

Reprints

Dr. Robert A. Black (Fellow), Chicago, Ill., three reprints;
Dr. Nathan Blumberg (Fellow), Philadelphia, Pa., one reprint;
Dr. Jacob M. Cahan (Fellow), Philadelphia, Pa., one reprint;
Dr. Mary Hoskins Easby (Fellow), Philadelphia, Pa., one reprint;
Dr. G. Philip Grabfield (Fellow), Boston, Mass., three reprints;
Dr. P. A. Gray (Fellow), Santa Barbara, Calif., twelve reprints;
Dr. Henry Joachim (Fellow), Brooklyn, N. Y., seven reprints;
Dr. Abel Levitt (Fellow), Buffalo, N. Y., one reprint;
Dr. Perry J. Melnick (Associate), Decatur, Ill., one reprint;
Dr. Paul H. Ringer (Fellow), Asheville, N. C., two reprints;
Dr. James W. Sherrill (Fellow) and Dr. E. F. F. Copp (Fellow), La Jolla, Calif., one reprint;
Dr. Walter H. Watterson (Fellow), LaGrange, Ill., one reprint;
Dr. Edward E. Woldman (Associate), Cleveland, Ohio, three reprints.

Grateful acknowledgment is also made of the receipt of the following directories as gifts to the College Library:

Medical Society of the State of New York, through Dr. Peter Irving (Fellow), New York City—"1937 Medical Directory of New York, New Jersey and Connecticut";
Bureau of Medicine and Surgery, U. S. N.—September 1, 1937, issue of the "Navy Directory."

Dr. Clement R. Jones (Fellow), Pittsburgh, Pa., has donated to the College Library an original copy of the Annals of Medicine, Volume I, No. 1, April, 1920. This was the first issue of the first journal sponsored by the American College of Physicians and the American Congress on Internal Medicine, but during the intervening years and changes of administration, all official copies of this issue had disappeared. It is an interesting addition to the College archives. First, it is a very attractive and well-printed journal. It contains the roster of the members of the American College of Physicians and of the American Congress on Internal Medicine up to March 1, 1920. In it appears the photographs of the Officers and Councilors of the College for that year, and photographs of the Convocation held on February 26, 1920, and of the Annual Banquet the same year, held at the Congress Hotel in Chicago. The contents of the journal, including a comprehensive article

by the first President of the College, the late Reynold Webb Wilcox, M.A., M.D., LL.D., D.C.L., F.A.C.P., on "The Field of Internal Medicine," were made up of presentations by Louis A. Turley, A.M., M.D., Ph.D., F.A.C.P., John A. Lichty, M.D., F.A.C.P., F. M. Pottenger, A.M., M.D., LL.D., F.A.C.P., E. H. Reudiger, A.B., M.D., F.A.C.P., Louis Faugeres Bishop, A.M., M.D., D.Sc., F.A.C.P., E. L. Tuohy, A.B., M.D., F.A.C.P., F. A. McJunkin, A.B., M.D., F.A.C.P., Hugo A. Freund, A.B., M.D., F.A.C.P., Bruce C. Lockwood, A.B., M.D., and Frank Smithies, M.D., Sc.D., M.A.C.P. Dr. Smithies was the Supervising Editor.

Motion Picture Reels

Mrs. Louise K. Smithies, widow of the late Dr. Frank Smithies, former Secretary-General and former President of the College, due to Dr. Smithies' long association with this College, has donated to the College Dr. Smithies' two 35 mm. reels showing his method of dilation of cardiospasm by the pneumatic expanding bougie. These motion picture films are available, on loan, to members of the College who may wish to show them.

The Twenty-Second Annual Session of the College

The Twenty-Second Annual Session of the College will be held in New York City, April 4 to 8, inclusive, 1938, with headquarters at the Waldorf-Astoria Hotel, 49th to 50th Streets, Park to Lexington Avenues. Dr. James H. Means, of Boston, as President of the College, will have charge of the program of General Sessions and Special Lectures. Dr. James Alex. Miller, of New York City, as General Chairman, will have charge of the program of Clinics and Round Tables.

Last spring, the Executive Offices sent out a brief postal questionnaire to determine the desires of members with respect to program arrangements and items, particularly the Special Lectures, Round Tables and Clinico-Pathological Conferences:

847 to 267 requested the retention of Special Lectures (these do not refer to the General Sessions, but to the series of special lectures given during the mornings, at the same time clinics are in session);
1046 to 101 favored the extension of the Round Table program;
1051 to 88 favored Clinico-Pathological Conferences on the program.

Many members sent in very helpful suggestions about titles and speakers, and the Program Committee is carefully considering them.

New York Hotel Rates—Hotel rates in New York City are, on the average, higher than in most other places. At the Waldorf, which is one of the world's finest hotels, a special convention rate has been obtained, beginning at $5.00 single (reduced from $7.00), and beginning at $7.00 double (reduced from $9.00). In the immediate neighborhood—in fact, within one square of the Waldorf—there are several other good hotels with varying rates. A list of such hotels may be obtained from the Executive Secretary of the College.

The Executive Committee, composed of the chairmen of the various committees for the New York Session, is as follows: Dr. James Alex. Miller, *General Chairman;* Dr. James Ralph Scott, *Vice Chairman;* Mr. E. R. Loveland, *Executive Secretary;* Dr. Robert A. Cooke, *Clinics;* Dr. Russell L. Cecil, *Round Tables;* Dr. Howard F. Shattuck, *Entertainment;* Dr. Peter Irving, *Publicity;* Dr. Edward P. Eglee, *Local Transportation;* and Dr. Willard J. Denno, *Auditorium.*

Testimonial to Dr. Pottenger

On September 26, 1937, former patients and friends of Dr. F. M. Pottenger (Fellow), Monrovia, Calif., gathered in the gardens of the Pottenger Sanatorium for a dual celebration; the annual home-coming of former patients, and the celebration of Dr. Pottenger's sixty-eighth birthday. More than 250 guests were present, many of whom came from points far-removed from the Pacific Coast, one from New York City.

Patients of the Pottenger Sanatorium who have been discharged as arrested or cured look upon themselves as "alumni" and refer to their "class." The oldest alumnus present was one who had been a patient in 1903.

Appropriately inscribed, a beautiful sundial was presented to Dr. Pottenger from the present patients. Other gifts were also presented and messages were received from all over the world.

Henry K. Mulford, known to a host of members of the American College of Physicians as the founder of the H. K. Mulford Company, Philadelphia, and internationally known in the field of biological research, died during October at the age of seventy-one, after an illness of several days. Mr. Mulford had more recently been the Director of the Research and Biological Laboratories of the National Drug Company, and President of the Mulford Colloid Laboratory. In connection with his early founding of the H. K. Mulford Company, he was directly in charge of making antitoxins and vaccines, the first in this country to interest himself in that line. He was graduated from the Philadelphia College of Pharmacy and Science in 1887.

Dr. Clifford E. Henry (Fellow), Minneapolis, Minn., has been advanced from the rank of commander to that of captain in the naval medical reserve corps. This rank is held by only four men in the country, and is next in line to that of rear admiral. Dr. Henry is Minnesota's senior naval medical reserve officer.

The Mississippi Valley Medical Society of which Dr. Harold Swanberg (Fellow), Quincy, Ill., is Secretary, offers a cash prize of $100.00, a gold medal and a certificate of award for the best unpublished essay on a subject of interest and practical value to the general practitioner of medicine. Entrants must be ethical licensed physicians, residents of the United States and graduates of approved medical schools. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society (September 28 to 30, 1938), the Society reserving the exclusive right to first publish the essay in its official publication, *The Radiologic Review and Mississippi Valley Medical Journal*. Contributions shall not exceed five thousand words, shall be typewritten in English in manuscript form, submitted in five copies, and must be received not later than May 15, 1938.

Dr. William B. Grayson (Associate), Little Rock, Ark., was recently re-appointed state health officer for a second term of four years.

Dr. William E. Gardner (Fellow), Louisville, Ky., was made President-Elect of the Kentucky State Medical Association for 1937–38 at its annual meeting during September.

Dr. Frank M. Stites, Jr. (Fellow), Louisville, was elected a Vice President. The 1938 meeting of the Association will be held in Louisville.

Dr. Hubert C. King (Fellow), Lakewood, Ohio, and Dr. Karl D. Figley (Fellow), Toledo, Ohio, are members of the subcommittee of the newly-organized Speakers' Bureau of the Ohio State Medical Association, formed for the purpose of assisting county and district medical societies in obtaining outside talent for their programs. It is anticipated that the facilities of the Bureau will later be made available for meetings of allied and lay groups.

Major General Charles R. Reynolds (Fellow), Surgeon General of the U. S. Army, addressed the annual "Mercy Day" celebration of the Mercy Hospital in Pittsburgh on September 23, his subject being "Medicine in the Military Service."

Dr. William D. Stroud (Fellow and Treasurer), Philadelphia, Pa., addressed the Forty-third annual meeting of the Utah Medical Association of Salt Lake City, September 2 to 4, on "Etiology of Cardiovascular Disease; Coronary Diseases Including Angina Pectoris; Clinical Efficacy of Digitalis Preparations."

Under the presidency of Dr. J. Morrison Hutcheson (Fellow and Governor), Richmond, Va., the Medical Society of Virginia held its Sixty-Eighth Annual Session at Roanoke, October 12 to 14.

A sectional meeting and dinner of the Fellows and Associates of the American College of Physicians was held at the Shenandoah Club in Roanoke on October 12 during the course of the State meeting. Dr. J. W. Preston (Fellow), Roanoke, was Chairman of the local committee on arrangements for the sectional College meeting.

Dr. Paul A. O'Leary (Fellow), Rochester, Minn., is Secretary General of the Tenth International Congress of Dermatology and Syphilology to be held in New York City during September, 1940.

Dr. Warfield T. Longcope (Fellow), Baltimore, Md., delivered the Gordon Wilson Lecture on "The Varieties of Hemorrhagic Nephritis and Their Prognostic Significance" before the Fifty-Fourth Annual Meeting of the American Clinical and Climatological Association in Baltimore, October 11 to 13.

Under the presidency of Dr. William H. Cade, Jr. (Associate), San Antonio, Tex., the Southern Psychiatric Association held its annual meeting at San Antonio, October 8 to 9. Among the invited guests on the program were the following: Dr. George T. Harding (Fellow), Columbus, Ohio—"Periodicity of the Manic-Depressive Psychoses"; Dr. C. Charles Burlingame (Fellow), Hartford, Conn.—"Can the Point of View and Technic of Private Practice Be Carried into the Mental Hospital"; and Dr. George R. Herrmann (Fellow), Galveston, Tex.—"Neurocardiac and Neurocirculatory Disorders."

Dr. Herman M. Baker (Fellow), Evansville, Ind., will start the new year as President of the Indiana State Medical Association on January 1, 1938.

Dr. Hugo A. Freund (Fellow), Detroit, Mich., has been appointed a member of the city Public Welfare Commission.

Under the presidency of Dr. George A. Young (Associate), Omaha, Nebr., the Omaha Mid-West Clinical Society held its fifth annual assembly, October 17 to 22.

Among the invited guest speakers were: Dr. William J. Kerr (Fellow and President-Elect), San Francisco, Calif.—"The Anxiety States in General Practice"; Dr. Hans H. F. Reese (Fellow), Madison, Wis.—"The Constitution and the Biochemical Evaluation of the Nervous Patient"; and Dr. Thomas Parran (Fellow), Surgeon General of the U. S. Public Health Service—"Syphilis and the Public Health."

Dr. William B. Porter (Fellow), Richmond, Va., was recently awarded the Jefferson Gold Medal of the Virginia Academy of Science.

Dr. Vincent J. Dardinski (Associate), Washington, D. C., has been appointed full time Pathologist and Director of the Laboratories of the Georgetown University Hospital. Dr. John R. Cavanagh (Associate), Washington, D. C., Associate Clinical Professor of Medicine at the University, will become Director of the Outpatient Department of the Hospital. Dr. Frank S. Horvath (Associate), Associate Professor of Clinical Medicine, will be Assistant Director and Supervisor of Student Instruction in the Outpatient Department of the Hospital.

Dr. Russell M. Wilder (Fellow), Rochester, Minn., addressed the clinical session of the New York Diabetes Association on October 15 on "Pathogenesis and Etiology of Diabetes."

Dr. Nelson W. Barker (Fellow), Rochester, Minn., has been elected Secretary of the Southern Minnesota Medical Association.

Under the presidency of Dr. Charles E. Sears (Fellow), Portland, Ore., the Oregon State Medical Society held its Sixty-Third Annual Session at Salem, October 21 to 23. Dr. Lester R. Dragstedt (Fellow), Chicago, Ill., was one of the guest speakers, his subjects being "Pathogenesis and Surgical Treatment of Duodenal Ulcer" and "Pathogenesis and Surgical Treatment of Acute Intestinal Obstruction."

Dr. Louis F. Bishop, Jr. (Fellow), gave a talk on "Exercise in the Treatment of Chronic Cardiovascular Disease" before the Section on Medicine of the 16th Annual Scientific and Clinical Session of the American Congress of Physical Therapy on September 22, 1937, in Cincinnati.

On Sunday October 2, 1937, Dr. Bishop, Jr., also gave a talk (on invitation) on "Is It Safe for the Heart Patient to Fly?" before the Ninth Annual and First International Meeting of the Aero Medical Association of the United States, Hotel Waldorf Astoria, New York, October 3, 1937.

Regional Meeting of Michigan Members

A regional meeting of the Michigan Fellows and Associates of the College was held in Detroit, November 17, under the Governorship of Dr. Henry R. Carstens. Dr. Hugh Freund of Detroit assisted in the arrangement of the program, and the Harper Hospital acted as host. Clinical presentations were given at the Harper Hospital from 4:00 to 6:30 p.m., followed by a social hour and dinner. Dr. James D. Bruce, Regent of the College, Ann Arbor, addressed the group on matters of interest about the College, and Dr. A. B. Brower, College Governor for Ohio, Dayton, gave an address on "Hypotension." A large and representative group was present.

OBITUARIES

LT. COL. LEROY T. HOWARD

Lieutenant Colonel Leroy T. Howard (Fellow), Medical Corps, U. S. Army, died suddenly in Washington, D. C., on September 30, 1937.

Colonel Howard, a native of the District of Columbia, was born October 27, 1888. He was a graduate of the Georgetown University, from which he received his medical degree in 1913. Following this he interned for one year in St. Francis' Hospital, Jersey City, N. J. He was commissioned a First Lieutenant in the Medical Reserve Corps on September 29, 1916, and shortly thereafter he was called to active duty and pursued a course of instruction at the Army Medical School, Washington, D. C., from October 14, 1916, to March 28, 1917. He was commissioned in the Regular Army as First Lieutenant, Medical Corps, on April 16, 1917, promoted to Captain March 28, 1917, Major May 27, 1918, and Lieutenant Colonel March 3, 1937. He was returned from duty in Hawaii March 29, 1937, on account of illness and was on sick leave pending retirement for disability at the time of his death.

Colonel Howard was a specialist in neuro-psychiatry and served in that capacity at several of the largest hospitals in the Army. During the World War he served in France. He had been a Fellow of the American College of Physicians since 1932.

W. L. Sheep, M.D., F.A.C.P.,
Colonel, Medical Corps, U. S. A.

DR. RICHARD BARRETT OLESON

Dr. Richard Barrett Oleson (Fellow), of Lombard, Illinois, died on August 6, 1937, at the Johns Hopkins Hospital. Death ensued as a result of a septicemia following a prostatic operation.

Dr. Oleson was born in Bloomington, Ill., in 1870. His preliminary education was obtained in the public schools of Bloomington, Columbus (Ohio), and Lombard. He completed his preparation for college at Wheaton College Academy, Wheaton, Ill. Later, he attended the University of Wisconsin. He received his degree of Doctor of Medicine from the Northwestern Medical School in 1893, and immediately thereafter served an internship of eighteen months' duration at the Cook County Hospital. For some years he was Medical Attendant at the Country Home for Convalescent Children, at Prince Crossing. He served one year as Clinical Assistant in the Dispensary of the Johns Hopkins Hospital, 1919–20.

For many years he practiced Internal Medicine, specializing in Gastroenterology, in Lombard. He was widely known throughout his neighborhood, and highly respected as a physician of exceptional ability and character. At one time he did postgraduate work at the Trudeau School of Tubercu-

losis, Saranac Lake, N. Y. He contributed a number of excellent articles to the literature, and was active in medical society work. He was a member of the Chicago Medical Society, the Illinois State Medical Society, the American Medical Association and was a Fellow of the American College of Physicians since 1922.

Dr. Oleson will be sorely missed in the community which has suffered this loss. For years he had given superior medical service to the people among whom he lived, and he enjoyed a wide reputation. The profession has lost an outstanding man who rendered excellent service to the people whose good fortune it was to have known him.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois.

ERRATUM

"The Acute and Subacute Pulmonary Involvement in Rheumatic Fever with Notes on the Complication of Basal Pulmonary Collapse" by Dr. Benjamin A. Gouley, pages 626-636, October ANNALS OF INTERNAL MEDICINE. The last four references in the text were not included in the reference list at the end of the article. They are as follows:

11. WENCKEBACH, K.: Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1935, viii, 32.
12. SCHOEN, R.: Die Pneumonose, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1935, viii, 94.
13. PARKER, F., JR., and WEISS, S.: Significance of lung changes in mitral stenosis, Am. Jr. Path., 1936, xii, 573.
14. EWART, W.: Practical aids in the diagnosis of pericardial effusion in connection with the question of surgical treatment, British Med. Jr., 1896, i, 717.